PHARMACEUTICAL ENGINEERING

THE OFFICIAL TECHNICAL MAGAZINE OF ISPE

NOVEMBER/DECEMBER 2014 VOLUME 34, NUMBER 6

Risk-Based Outsourcing

Direct to Patient IMPs

Isolator Design

Reshoring

Cleaning Process Optimization

Supply Chain Integrity

Standardized Extractables Protocol

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NOVEMBER/DECEMBER 2014
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facilities and equipment

production systems

regulatory compliance

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Welcome to this edition of *Pharmaceutical Engineering*, which looks at the evolving area of outsourcing of manufacturing, including the selection of the most appropriate organization and the use of outsourcing to ease the reshoring of manufacturing to the US.

The lead article by Chatterjee notes that growth in the biotechnology field along with increased emphasis on science-based technology and the emergence of novel drug delivery providers has transformed the prerequisites for selecting a Contract Manufacturing Organization (CMO). The reliance of many virtual companies on CMOs, along with experience gained of contract manufacturing by industry, means that the role of CMOs has evolved significantly, and that a methodical approach is therefore required to ensure selection of the most appropriate organization.

The article recognizes that the use of risk-based methods can greatly assist structured decision-making and reduce the subjectivity that may creep into complex decisions. Through a case study, the article discusses the application of a risk-based method to assist in the objective evaluation of alternative contract service providers so the most appropriate organization is selected to meet particular goals.

Danna considers the current trend of reshoring of manufacturing to the US and some of the factors fueling that trend. He covers some of the challenges of reshoring and how these can be eased by partnering with the right domestic outsource organization. Again, the importance of selecting the right partner is highlighted and discussed.

In wider developments, the increasingly innovative solutions being developed to recruit and retain patients for clinical studies is likely to lead to an increasing need for shipment of clinical trial supplies direct to patient homes, as explored by Sadler-Williams, et al. An overview of the regulatory environment is given, along with potential supply strategies and practical issues around shipping clinical supplies direct to patient homes.

Scalva, et al, present an approach for implementing an improved automated cleaning process, which significantly reduced the overall duration for decontamination and cleaning. The project discussed was governed by Lean Six Sigma (LSS) principles, and the cleaning process was redeveloped at the bench scale and then transferred and tested at a pilot scale, before being translated to the manufacturing floor.

An overview of the regulations and international developments on quality and supply chain integrity of pharmaceutical excipients is provided by Chan, et al, with an analysis of the challenges faced by regulatory authorities and recommendations to improve the excipient control framework.

Finally, a consensus standardized extractables testing protocol for single use systems in biomanufacturing is presented by Ding, et al,. A proposal outlining standardized methods for extractables testing of SUS components was developed by the Extractables Work Group of the BioPhorum Operations Group (BPOG) and is based on results of a survey of 17 major BPOG member companies across 26 sites. The protocol covers the methods used for extractables testing studies, including sample preparation, extraction conditions, recording test article sampling conditions, and reporting data from analysis of extracts.

I am also pleased to present an article by Barbu and Zwick, originally published in the Aseptic E-supplement August 2014, which discusses the selection, design, and validation of isolators to be used by the Musculoskeletal Transplant Foundation.

As always, I welcome your feedback – email me at ghall@ispe.org.

Gloria Hall
Editor, *Pharmaceutical Engineering*

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Strategies for Assessing and Managing Risk

by Roger Nosal, Chair, *Pharmaceutical Engineering* Committee

Like other regulated businesses, the pharmaceutical industry is focused on appropriately managing risk. From the facilities we construct to the regulatory submissions we make, our ability to address and manage risks can be translated into confidence in quality. Once that confidence is earned and sustained it can be a competitive advantage; however, failure to manage risks can and often does result in rapid loss of confidence.

Everyone sees risk differently. For some the word "risk" conjures images of hazards and dire consequences. For others the word "risk" poses a challenge.

In all cases, one's perception of risk is intuitively defined by rational doubt and/or irrational fear, primarily based on individual experience.

In the pharmaceutical business, dealing with risk is inherent in the development, manufacture and maintenance of medicines on the market. There are no absolutes. The risks associated with pharmaceuticals largely govern the work required to demonstrate and ensure product quality. While science certainly provides a reasonable level of confidence, the element of uncertainty forces us to make judgments based on our collective experiences.

In 2015, *Pharmaceutical Engineering* will focus each of its issues on various elements of risk with particular emphasis on strategies for assessing and managing risk with respect to various aspects of pharmaceutical development and manufacturing. We're proposing the following focus areas for each issue:

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Focus Areas

- Definition of Risk
  - General Approach to Risk in Accordance with QRM (ICH Q9)
  - Risk Assessments – Prospective vs. Retrospective
  - Risk as a Function of Product Lifecycle
  - If a Risk is Mitigated by a Control is it Still a Risk?
  - Retrospective Risks – Legacy Products
- Applying Quality Risk Management to Product Development and Pharmaceutical Manufacturing
  - Risks Associated with Supply Chain Complexity

  - Residual Risk
  - Minimizing Risk through Introduction of RTRt, Continuous Processing, etc.
  - Managing Risks for Expedited Regulatory Submissions – Breakthrough Therapy Designation
  - Risk Associated with Clinical Protocols

- Risks Associated with Manufacturing Facilities
  - How Manufacturing Plant Design can Mitigate Risk?
  - Mitigation of Risks for Sterile Manufacture
  - Environmental Risks

- Risks Associated with Pharmaceutical Quality Systems
  - Lifecycle Change Management
  - Knowledge Management – Risk Assessments
  - Site Transfers
  - Quality Metrics

- Risks Associated with Product Performance
  - Risks and Absence of Bio-relevance
  - Patient Compliance, Product Compatibility and In-Use
  - Devices

- Risk-Based Regulatory Review
  - Benefit vs. Risk
  - Clinically Relevant Specifications
  - Comprehensive Control Strategy
  - Regulatory Commitments and Post Approval Change Management Protocols

We encourage readers and members of ISPE to contribute relevant articles for each of these focus areas.

Call for Articles

Pharmaceutical Engineering, ISPE's technical magazine, is looking for subject matter experts in the global pharmaceutical industry with knowledge of the latest scientific and technical developments, regulatory initiatives, and innovative solutions to real life problems and challenges who can contribute application articles and case studies.

Special features and guest editorials will be considered that focus on new technology, contemporary quality management practices, and production innovation.

New Departments include: facilities and equipment, information systems, product development, production systems, quality systems, research and development, supply chain management, and regulatory compliance.

Industry Hot Topics
In addition to the Departments, each issue of *Pharmaceutical Engineering* will feature industry relevant hot topics, including biosimilars, breakthrough therapies, next generation manufacturing, quality metrics, quality risk management, supply chain integrity, and sustainability.

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Risks Associated with Product Performance
Manuscripts Due: 7 May 2015 Publishes: 21 Sep 2015

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Manuscripts Due: 9 Jul 2015 Publishes: 23 Nov 2015

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Case Study: Applying a Risk-Based Decision Making Framework for Outsourcing

by Bikash Chatterjee

This article will discuss the application of Analytic Hierarchy Process (AHP) and Pairwise Comparison as a tool to assist in the objective evaluation of alternative contract service providers.

The Contract Manufacturing Organization (CMO) landscape has come into being and progressed over the last decade. Growth in the biotechnology field with increased emphasis on science-based technology and the emergence of novel drug delivery providers has transformed the prerequisites for selecting a CMO.

Virtual companies in particular rely heavily on CMO capabilities and expertise to meet their business objectives. In the 2014 Annual Contract Pharma Outsourcing Survey,1 75 percent of virtual pharmaceutical companies reported they would most likely outsource their clinical manufacturing, while 88 percent planned to outsource their API manufacturing. The central role CMOs are playing in determining business success requires a more methodical approach to be taken to ensure the CMO selection fits your company's business model.

Evolving Role of Contract Service Providers

The role of contract service providers also has changed dramatically over the last decade when the move to outsourcing manufacturing to the emerging markets was nearly a mandatory component in most organizations' business strategy. Since these early experiences, the industry has gained greater clarity with regard to the characteristics and metrics required to ensure a successful and effective relationship with a contract service provider.

One dilemma facing a team of evaluators in attempting to rank CMOs is that, based on Figure 1, the differences between criteria priority are small, making it appear that all criteria are important and further complicating any decision-making process.

Historically, evaluating a CMO revolved purely around benchmarking its execution performance in key supply chain metrics such as On-Time-In-Full (OTIF) delivery performance, Right-the-First-Time (RTF), and cycle-time, etc. Today, however, most organizations refer to their contract service providers as partners. The 2014 Annual Contract Pharma Outsourcing Survey respondents from across the industry listed elements as considerations - Figure 1. Each category was ranked on a scale from 1 to 5 with 1 being not important and 5 being very important.

Structured Decision Making

Based on the categories cited in Figure 1, it doesn't take long to make a simple problem a complex one when all factors to be considered are introduced into the decision-making process. The challenge is not necessarily to choose the best contract service provider, but to choose the one most adapted to the goals of the business problem to be addressed. Risk-based frameworks are excellent vehicles for driving decision making because most risk analysis tools require some form of ranking table for the evaluators to quantify the risk. This common basis for evaluation greatly reduces the subjectivity that can creep into complex decisions.

There are a number of risk-based tools that can effectively

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assist in providing a structured approach to decision-making, such as Pugh Matrices, Decision Tree Analysis, Analytic Hierarchy Process (AHP), and Pairwise Comparison analysis. This article will discuss the application of AHP and Pairwise Comparison as a tool to assist in the objective evaluation of alternative contract service providers.

Analytic Hierarchy Process and Pairwise Comparison

AHP is a method to support multi-criteria decision-making, and was originally developed by Professor Thomas L. Saaty,2 while directing research projects in the U.S. Arms Control and Disarmament Agency. It was developed as a reaction to the lack of a common, easily understood and easy-to-implement methodology to enable the taking of complex decisions. The simplicity and power of AHP has led to its widespread use in every part of the world. The application of AHP has found use in business, government, social studies, R&D, defense and other domains involving decisions in which choice, prioritization or forecasting is needed.

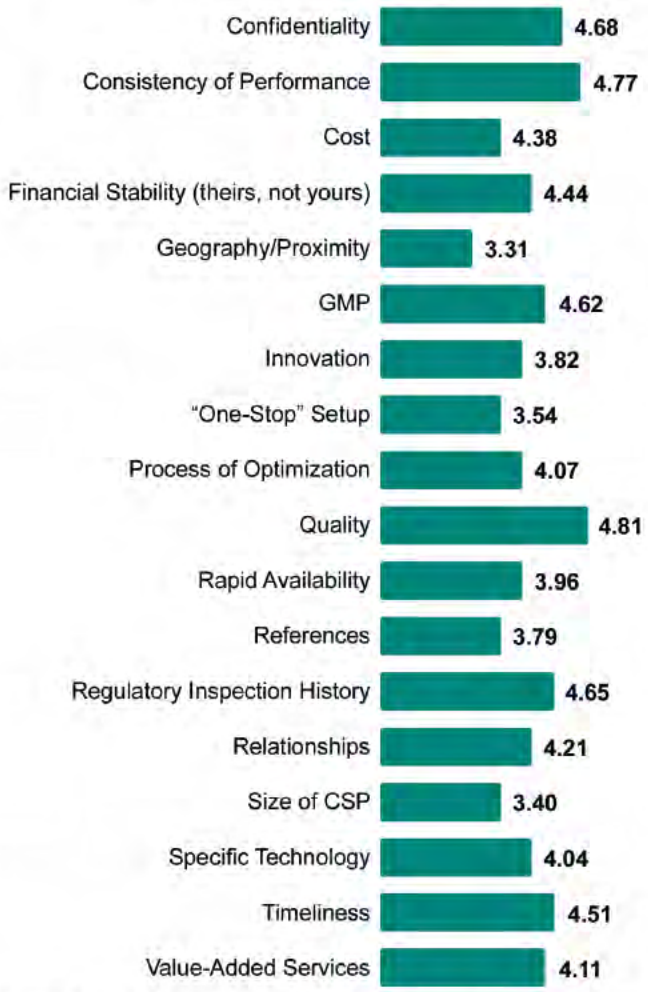

Figure 1. 2014 Annual Contract Pharma outsourcing survey.

Using AHP requires that the alternatives to evaluate be structured as a hierarchy. This drives the determination of evaluation/decision criteria and requires that each criterion be analyzed by identifying what is most significant with respect to the decision objective. Using pairwise comparisons helps to discover and correct logical inconsistencies. The method also allows to "translate" subjective opinions, such as preferences or feelings, into measurable numeric relations. AHP helps to make decisions in a rational way. AHP derives ratio scales from paired comparisons of criteria, and allows for some small inconsistencies in judgments. In addition to subjective opinions, inputs can be actual measurements. From this analysis, priorities (weightings) and a consistency ratio will be calculated.

Case Study: Choosing a Contract Manufacturer

To illustrate the application of AHP and pairwise comparison, a case study will be presented in which a firm has made the decision to outsource its manufacturing to a contract manufacturing operation. The product is a two-component capsule in which one active ingredient is a controlled release formulation, while the second component is an immediate release component. The drug is coated onto sugar spheres using a Wurster coating process. The business objectives linked to this program decision are:

1. Ability to support U.S. and European market introduction simultaneously
2. Scalable profit model, volume driven, predicated on escalating manufacturing batch sizes and efficiencies

Given these business objectives, small CMOs that were capacity-constrained were immediately eliminated. To move forward, it was essential to establish a set of criteria to evaluate each candidate CMO. The following criteria were established for evaluating them:

1. Understanding of Wurster technology and capsule manufacturing
2. Geography/proximity
3. Cost of services
4. Equipment and plant available capacity
5. Confidentiality
6. Regulatory inspection
7. Special services: analytical, micro lab, supply chain, and distribution support
8. Internal regulatory expertise for U.S. and European submission process
9. Technical scale-up experience

For the purpose of this example, the top four criteria will be evaluated against the three CMO alternatives.

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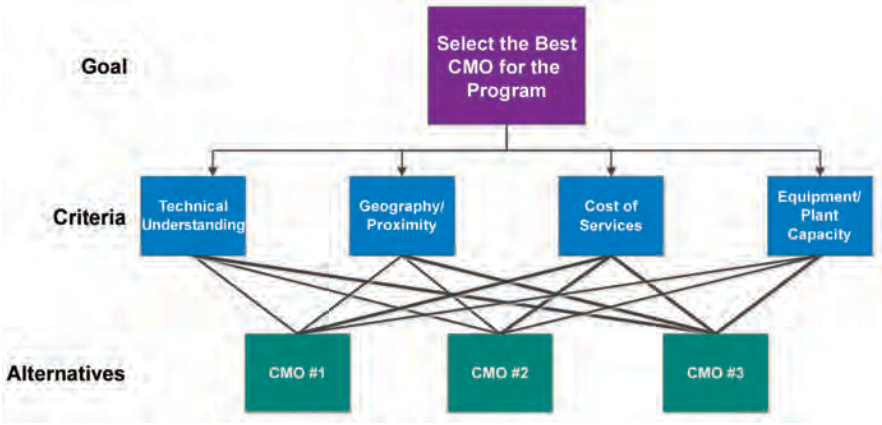

Figure 2. Alternative CMO AHP graphical representation.

Applying AHP

The first step in applying AHP is to capture the alternatives in a graphical format so all decision makers understand the specific questions at hand. For this example, three candidate CMOs were identified that could satisfy all nine criteria to some level. CMO #1 was based in the U.S., CMO #2 in the UK, and CMO #3 in China. The AHP Hierarchy is shown in Figure 2.

Pairwise Comparisons: Alternatives vs. Criteria

Within the AHP hierarchy, it is important to establish the priorities for each element. Priorities are the numbers associated with the nodes of an AHP hierarchy. They represent the relative weights of the nodes in any group. Similar to probabilities, priorities are absolute numbers ranging from 0 to 1 they are unitless and reflect the weight of the element being evaluated. For example, criterion with a priority of 0.300 has three times the weight of criterion with a priority of 0.100.

The team can use whatever scale it deems appropriate for assigning priorities, including importance to the program's success, preference, risk tolerance, etc. AHP is intended to provide a structured framework for this discussion. Similar to ranking tables in an FMEA, the value in establishing priority values is the common definitions assigned to the evaluation by the team, moving qualitative criteria to semi-quantitative.

Priorities of the goal, the criteria, and the alternatives are closely related, but need to be considered separately. By definition, the priority of the goal is 1.000. The priorities of the alternatives should always add up to 1.000. Things can become complicated with multiple levels of criteria, but if there is only one level, their priorities should also add to 1.000.

The priorities will be derived from a series of measurements: pairwise comparisons involving all the nodes. The nodes at each level will be compared, two by two, with respect to their contribution to the nodes above them. The results of these comparisons will be entered into a matrix which is processed mathematically to derive the priorities for all the nodes on the level.

The comparisons can be made in any sequence, but in this example we will begin by comparing the alternatives with respect to their strengths in meeting each criterion. Then we'll compare the criteria with respect to their importance to reaching the goal.

Details of the pairwise calculation are given in Saaty's landmark book.3 The Consistency Ratio indicates the amount of allowed inconsistency (0.10 or 10%). Higher numbers mean the comparisons are less consistent. Smaller numbers mean comparisons are more consistent. CRs above 0.1 means the pairwise comparison should be revisited or revised.

We will make three pairwise comparisons with respect to each Criterion: CMO #1 vs. #2, CMO #1 vs. #3, and CMO #2 vs. #3.

AHP uses matrix algebra to arrive at a mathematically optimal solution. AHP also uses actual measures like price, counts, or subjective opinions as inputs into a numerical matrix. The outputs include ratio scales and consistency indices derived by computing eigenvalues and eigenvectors. Saaty allowed some measures of inconsistency (common with subjective human judgment) when applied to the logic of preferences. Inconsistencies arise when comparing three items, A, B, and C.

For example, if item A is more preferred over item B, and item B is more preferred over item C, by the transitive prop-

AHP Scale of Importance for comparison pair (aij)	Numeric Rating	Reciprocal (decimal)
Extreme Importance	9	1/9 (0.111)
Very Strong to Extremely	8	1/8 (0.125)
Very Strong Importance	7	1/7 (0.143)
Strongly to Very Strong	6	1/6(0.167)
Strong Importance	5	1/5(0.200)
Moderately to Strong	4	1/4(0.250)
Moderate Importance	3	1/3(0.333)
Equally to Moderately	2	1/2(0.500)
Equal Importance	1	1 (1.000)

Table A. Preferences made on 1-9 scale.[2]

Intensity of Importance	Definition	Explanation
1	Equal importance	Two elements contribute equally to the objective
3	Moderate importance	Experience and judgment moderately favor one element over another
5	Strong importance	Experience and judgment strongly favor one element over another
7	Very strong importance	One element is favored very strongly over another; it's dominance is demonstrated in practice
9	Extreme importance	The evidence favoring one element over another is of the highest possible order of affirmation
Intensities of 2, 4, 6 and 8 can be used to express intermediate values. Intensities of 1.1, 1.2, 1.3, etc. can be used for elements that are very close in importance.		

Table B. Pairwise comparison ranking table.

erty, Item A should be more preferred over item C. If not, the comparisons are not consistent. Measures of inconsistency set AHP apart from other multi-criteria methods like goal programming, multi-attribute utility theory, conjoint analysis, or choice experiments. Individuals and groups use the AHP preference scale in Table A to form the comparison matrices.

The paired comparison scale between the comparison pair (aij) of two items (item i and item j) is as follows: (item i) 9-8-7-6-5-4-3-2-1-2-3-4-5-6-7-8-9 (item j). The preference scale for pair-wise comparisons of two items ranges from the maximum value 9 to 1/9 (0.111 in decimal from). Let aij represent the comparison between item-i (left) and item-j (right). If item-i is 5 times (strong importance) more important than item-j for a given criteria or product, the comparison aji = 1/aij = 1/5 (0.200) or the reciprocal value for the paired comparison between both items.

For each comparison, the team will first determine which member of the pair is weaker with respect to the criterion under consideration. Then they will assign a relative weight to the other candidate CMO. They will use the AHP fundamental scale described below in Table B to assign the priority values

By processing this matrix mathematically, the AHP derives priorities for the candidates with respect to each criterion. These values can be calculated in many ways, including by hand, with a spreadsheet program, or by using specialized AHP software. They are shown below to the right of the matrix, along with a consistency factor computed by the specialized AHP software that was used to process the data. A rule of thumb in assigning importance for each pairwise comparison is to result in a consistency factor of < 10%. The calculations for this example were made using an Excel spreadsheet equipped with an AHP macro. In this spreadsheet, only the red boxes need to be filled in as the reciprocal values for their corresponding comparison cells were automatically filled in. The meaning of the reciprocal value is the commensurate inferiority value for the pair, e.g., 1/3 is moderately less important than 3. The result of each comparison is shown in Tables C to F.

	CMO #1	CMO #2	CMO #3	AHP Value
CMO #1	1	5	3	0.650
CMO #2	1/5	1	1/3	0.116
CMO #3	1/3	3	1	0.234
Consistency Check		4%- OK		

Table C. Pairwise Comparison Matrix: Alternative CMOs vs. Technical Expertise.

	CMO #1	CMO #2	CMO #3	AHP Value
CMO #1	1	5	3	0.677
CMO #2	1/5	1	1/3	0.231
CMO #3	1/7	1/3	1	0.092
Consistency Check		1%- OK		

Table D. Pairwise Comparison Matrix: Alternative CMOs vs. Geography/Proximity.

	CMO #1	CMO #2	CMO #3	AHP Value
CMO #1	1	2	1/4	0.183
CMO #2	1/2	1	1/6	0.112
CMO #3	4	6	1	0.705
Consistency Check		1%- OK		

Table E. Pairwise Comparison Matrix: Alternative CMOs vs. Cost of Services.

	CMO #1	CMO #2	CMO #3	AHP Value
CMO #1	1	3	1/3	0.234
CMO #2	1/3	1	1/5	0.116
CMO #3	3	5	1	0.650
Consistency Check		4%- OK		

Table F. Pairwise Comparison Matrix: Alternative CMOs vs. Equipment/Plant Capacity.

	Technical Expertise	Geography/ Proximity	Cost of Services	Equip/Plant Capacity	AHP Value
Technical Expertise	1	7	3	5	0.592
Geography/ Proximity	1/7	1	1/5	1/2	0.070
Cost of Services	1/3	5	1	5	0.239
Equipment/ Plant Capacity	1/5	2	1/5	1	0.099
Consistency Check			9%- OK		

Table G. Pairwise Comparison Matrix: Alternative CMOs vs. Program Goal.

Criterion	Priority vs. Goal (PVG)	Alternative	AHP Value (A)	PVG (B)	Final AHP Value (C)
Technical Expertise	0.592	CMO #1	0.650	0.592	0.385
		CMO #2	0.116	0.592	0.069
		CMO #3	0.234	0.592	0.138
		TOTAL	**1.000**		**0.592**
Geography/ Proximity	0.070	CMO #1	0.677	0.070	0.047
		CMO #2	0.231	0.070	0.016
		CMO #3	0.092	0.070	0.006
		TOTAL	**1.000**		**0.069**
Cost of Services	0.239	CMO #1	0.183	0.239	0.049
		CMO #2	0.112	0.239	0.028
		CMO #3	0.705	0.239	0.168
		TOTAL	**1.000**		**0.245**
Equip/Plant Capacity	0.099	CMO #1	0.234	0.099	0.023
		CMO #2	0.116	0.099	0.011
		CMO #3	0.650	0.099	0.064
		TOTAL	**1.000**		**0.098**

Table H. AHP and pairwise comparison calculations.

	Priority with Respect to the Goal				
Alternative	Technical Expertise	Geography/ Proximity	Cost of Services	Equip/Plant Capacity	AHP Value
CMO #1	0.385	0.047	0.049	0.023	0.936
CMO #2	0.069	0.016	0.028	0.011	0.124
CMO #3	0.138	0.006	0.168	0.064	0.376
Totals	0.592	0.069	0.245	0.098	1.004

Table I. Final AHP and pairwise comparison analysis.

Pairwise Comparisons: Alternatives vs. Goal

The reality in any decision is that all criteria for selection are not weighted equally. This is often the central issue that derails most decisions. To circumvent this, the next step is to weight the importance of each criterion in terms of achieving the goal of selecting the best CMO for the program. The same ranking table is used to weight each criterion and is summarized in Table G.

Table G shows the same reciprocal pairing defined in Table A by Saaty. A ranking of 7 for geographical/proximity on the X axis results in its reciprocal of 1/7 on the y axis. To calculate the AHP value (sometimes called the priority vector), the Excel program calculates the eigenvector as follows:

1. Consider $[Ax = l_{max}x]$ where:
   a. A is the comparison matrix of size n × n, for n criteria, also called the priority matrix.
   b. x is the eigenvector of size n × 1, also called the priority vector.
   c. l_{max} is the eigenvalue, $l_{max} \in \Re >$ n.
2. To find the ranking of priorities, namely the eigenvector X:
   a. Normalize the column entries by dividing each entry by the sum of the column.
   b. Take the overall row averages

Assembling the Final Analysis

Now that we know the priorities of the criteria with respect to the goal, and the priorities of the alternatives with respect to the criteria, we can calculate the priorities of the alternatives with respect to the goal. This is a straightforward matter of multiplying and adding, carried out over the whole of the hierarchy. The calculation is shown in Table H. For each criterion, the final AHP value is calculated as A × B = C. Based upon these calculations, the final analysis is shown in Table I.

The beauty of AHP is it does not allow inconsistent assessments between alternatives. They can be wrong, but they will be consistently wrong. As in any process, the decision is only as good as the data provided. Garbage in, garbage out.

Conclusion

Based upon the analysis, CMO #1 is the best selection for the program goal with CMO #3 second and CMO #2 third. By following the AHP process, all participants were allowed to provide both judgmental and quantitative input during the evaluation process. Most importantly, the logic driving the decision is well documented and can be revisited and explained by the team or any other concerned stakeholders who may wish to better understand the selection process.

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Establishing and Managing Processes Enabling Delivery and Returns of Investigational Medicinal Products (IMPs) to Patient's Homes

by Massimo Eli, Catherine Hall, Marianne Oth, PhD, Adrian Peskett, and Esther Sadler-Williams

This article overviews the regulatory environment and the potential supply strategies for shipping clinical supplies Direct to Patient (DTP) homes.

The clinical trial environment is expanding. Many sources have documented that in order to meet regulatory demand more studies are 'going global' and have an increasing number of countries included. Studies are increasing in duration and patients are participating in studies for longer. Additionally, the portfolio of products being investigated is changing with more emphasis on biological products.

However, data suggests that while the number of trials being conducted worldwide is increasing, the number of sites is remaining relatively constant.[1] Moreover, 83% of US sites only participate once in a clinical trial suggesting that there is increasing pressure for involvement for new studies on "good clinical sites."[2] Additionally, there is an increasing interest in undertaking "remote" or "e" clinical trials where most or part of the clinical protocol assessments are undertaken away from the clinical site.

Patients themselves are becoming more knowledgeable about medication they are taking, while at the same time they are looking for flexibility. A recent ISPE survey found that 78% of patients would find it helpful to have their clinical trial medication delivered to their homes rather than having to visit an investigator site. Interestingly, this finding was much more prevalent among the younger demographic who may be more time poor.[3]

In some countries, patients may have to travel long distances to visit clinical sites and this can influence their willingness to comply with site visits and hence the clinical protocol. Product stability also may be a concern in these situations for temperature sensitive products, because unless suitable transportation containers are provided to the patient, there is the risk that the storage conditions for the product may be compromised on the return journey to the patient's home.

Evidence from contributors to this article suggests that many clinical sites are already shipping clinical trial medication direct to patients on an "ad hoc" basis. This is a concern/consideration for the sponsor who is ultimately accountable as processes must be appropriately documented. Implementation of controlled solutions is therefore preferable.

Benefits in employing a Direct to Patient (DTP) shipping solution may include those shown in Table A.

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Beneficiary	Benefit
Patient	• Supports patients who have long/difficult travel to site • May eliminate need and burden of transporting large returns back to site • May prevent treatments/dosing being missed • Assists those with disabilities or other health issues that impacts their ability to travel • Supports patient lifestyle, e.g., work travel or holidays • Reduced travel costs
Site	• Simplified processes • Reduced storage burden • Possible to increase visit windows
Trial	• Increased patient retention • Improved patient compliance/ adherence • Manages the "last mile," full end to end control of product/stability right to the end users • Optimized drug accountability and returns • Reduced waste

Table A. Direct to Patient (DTP) shipping solution benefits.

Definition

There are two possible supply strategies when considering shipping clinical trial supplies direct to patient's residences.

- **Site to Patient:** in this scenario, supplies are still shipped via the investigative site, but then a specialist courier manages the ultimate distribution to the patient's home.
- **Depot to Patient:** in this scenario, IMP is shipped directly to the patient homes from either the original packaging/distribution facility or regional/country depots.

Both of these strategies will be discussed in this article although it should be recognized that even if a site to patient shipment strategy is permitted by local country regulations, these same regulations may not permit direct depot to patient shipments.

Regulatory Overview

There are very few clear regulatory references to Direct to Patient (DTP) and thus it is always best to be transparent to authorities and ethics review boards regarding such procedures in a trial application. Clearly, there is no single strategy that can fit all situations; however, there may be inclusion/exclusion criteria. For example, in the case of "take home" drugs, this approach may be limited by the hazardousness of the product, e.g., it is not likely to be appropriate for controlled substances. To date, only a few companies have implemented this type of distribution strategy for some clinical protocols in a restricted number of countries.

An increasing number of countries are becoming more "open" to sponsors employing a DTP strategy and as it has been already stated, early dialogue with the regulatory authorities/Ministry of Health (MOH) is recommended. The acceptance of this approach varies depending on the protocol and planned supply chain and one country that initially may, based on missing or incomplete study information, decline this strategy, later may accept DTP when fully recognizing the patient benefits.

US Regulations

Investigator responsibilities are described in the US regulations, (for example, 21 CFR 312.60-312.69) where it is mentioned that the clinical investigator "is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care." This statement could allow the interpretation of providing the drug "directly" to the trial subjects. Contrary to this, 21 CFR 312.61 seems to challenge the possibility to "mail" the

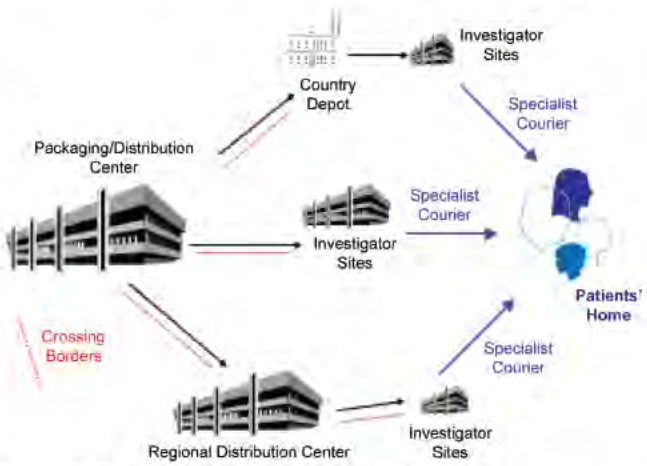

Figure 1. Distribution Network for DTP from site.

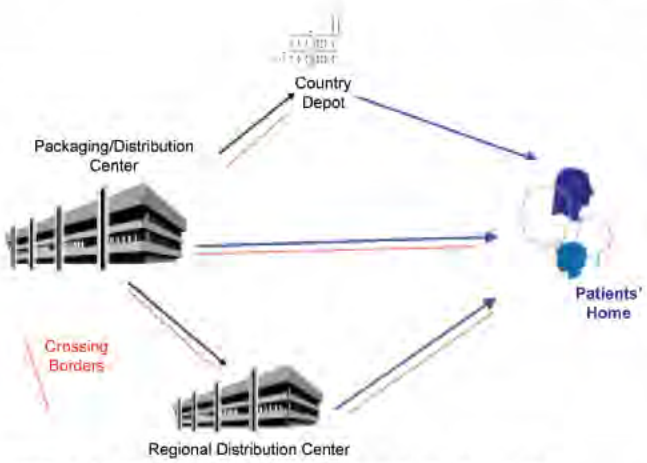

Figure 2. Distribution Network for DTP; not via clinical site.

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clinical trial supplies to the patient, as it requires that "an investigator shall administer the drug only to subjects under the investigator's personal supervision or under the supervision of a sub-investigator responsible to the investigator."

The FDA is concerned that the investigator:

- May lose control on the product and its quality (e.g., controlled temperature storage)
- May supply the drug to a person not authorized to receive it
- May not keep appropriate documentation.

The FDA does permit that in rare circumstances (e.g., distance from site, difficulty to travel), the drug could be dispensed via a family physician or local pharmacy, but this must still occur under direction from the investigator.

In addition, it would be prudent also to consider any Health Insurance Portability and Accountability Act (HIPAA) implications as HIPAA does mandate procedures for protecting the privacy of individual's health information and thus is applicable to patient/trial subjects.[4]

However, acceptance of DTP practices within the US is gaining more widespread acceptance. If the DTP process is described in the protocol in addition to the ethics committee submission/patient informed consent, as the approver of the clinical trial, FDA regulations should take precedence over any state regulations with respect to the approval of that clinical trial, as long as the investigator is still dispensing the IMP. However, it would be wise to consider any applicable individual US state laws that may need to be complied with, particularly in the case of any proposed strategy that did not involve the clinical site directly with dispensing IMP. For example, the sponsor would need to consider the laws in the state in which the dispensing facility is located, as well as the laws in the states into which the drugs are shipped.

EU Regulations

In the European Community, the recently issued EU Clinical Trial Regulations 536/2014, (which repeal the current Clinical Trial Directive 2001/20/CE), there is no mention of a DTP option. It states that IMP shall be traceable.[5] However, there are other laws and regulations throughout the EU that may prevent a manufacturer or wholesaler from distributing a medicinal product directly to a patient's home (e.g., German Drug Law Arzneimittelgesetz (AMG)), so such laws would need to be considered.[6]

In the MHRA Good Clinical Practice Guide,[7] the chapter related to storage and distribution makes a clear reference to the possibility of "Supply of Investigational Medicinal Products by Post" either as a pre-planned activity or in special circumstances with the major objective of facilitating patient accessibility to drugs and treatment compliance. The guide suggests that if clinical trial supplies are to be shipped/posted to patients, strong attention needs to be paid to:

- Compliance to storage requirements
- Assurances of a documented chain of custody
- GCP compliant drug accountability procedures

These details and processes would be subject to audit if DTP was employed for a study as part of any MHRA GCP audit of the clinical site or sponsor. Critical consideration must be given to the prescription being compliant with applicable laws and regulations at the point of dispensing if DTP models that do not use an investigator site are used.

In accordance with the above guidance, several websites of medical schools, National Health Service (NHS) hospitals and institutions describe the DTP practice as a viable option, particularly for studies where the same institution is also the sponsor of the trial. In general terms, it is a common understanding that the act of drug "dispensation" is "usually" performed by a pharmacist (or otherwise qualified individual) unless a differing prior agreement is in place with the pharmacy.

In collecting benchmarking information from the ISPE IP COP global community, extremely variable results were obtained with different justification for use of DTP. Some examples include:

It is well recognized that the number of clinical studies is growing and sponsors are increasingly turning to innovative solutions to recruit and retain patients. Patients themselves are requesting options for study participation that fit their clinical trial involvement around their lifestyle.

Although shipment of clinical trial supplies direct to patient homes is a relatively new concept, it is an option that is likely to grow in use to support the increasingly challenging and changing environment of clinical supplies. Until recently, this technique has been employed on an "emergency" or ad-hoc basis often without documented procedures or sponsor control. In addition to the potential benefits to the patient, the study site and the overall trial of a direct to patient shipment strategy for clinical supplies, the growing shift toward "virtual" or home based trial participation including home administration of clinical supplies by study nurses, will also fuel the demand for this type of approach.

This article provides an overview of the regulatory environment and potential supply strategies and practicalities for shipping clinical supplies direct to patient homes.

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- There are countries considering that the IMP can only be administered under physician's care so the "act" of giving the drug to the subject should be undertaken by the investigator.
- Some countries could allow the delivery from investigator sites to patient home only as a deviation to current legislation and so it should be described and approved in the protocol documentation.
- A country describes in their legislation that the IMPs "must" be received, from the sponsor, by the investigator or site pharmacist with the aim of prohibiting alternative supply chains

In all the cases referenced, DTP is applied to IMP shipments going from the investigator site to the subject, so the step of having the drug arriving at the clinical site is always fulfilled.

The alternate scenario of having the IMP shipped from the sponsor's depot directly to the subject home seems not to have been utilized to any extent as the task team found that a general requirement of the respective country's laws is the involvement of a "pharmacist." However, even considering to have (and document) a pharmacist performing the "order dispensation" of the IMP to the patient's residence from the depot, it is likely that a risk assessment and/or some form of formal agreement will need to be in place between the investigator sites and the depot's pharmacist, as each clinical site Principal Investigator (PI) has the overall responsibility for his/her patients.

There are some other aspects that should be considered in the overall objective of fulfilling general regulation requirements where they apply:

- Ensure appropriate description of the DTP distribution strategy in the protocol and obtain upfront approval from competent authorities to guarantee it won't be interpreted as Good Clinical Practice (GCP) non-compliance/protocol deviation
- Ensure correct information to the subjects and acceptance about the planned distribution approach (Ethics Committee approval and subject informed consent)
- Ensure appropriate control and GCP compliance for confidential information, like patient home address and contact details
- Ensure compliance with any applicable local laws and regulations

Practicalities of Direct to Patient (DTP) IMP Management

As described above, there are two main supply chain paths for delivery. First is to provide a route from a clinical site to the patient location, the second is to provide a route from a distribution depot to the patient location. In either case, the sponsor supply chain must be designed to provide clear chain of custody from an order by the site investigator to the delivery to the patient. The distribution route should resource personnel trained in GMP and GCP procedures and chain of custody documentation. For depot to patient, this is especially important.

Typically, the patient will visit the investigative site for the initial dispensation of study supplies and thus it is usual for only re-supplies to be provided direct to the patient's residence. As mentioned previously, depot to patient delivery is less common as local pharmacy laws and regulations or Ethics Committee interpretations of GCP may prohibit such a delivery option. In practice, the site investigator must place an order for the supplies to be sent to the patient. This order then is received at the distribution depot and documented to be from the investigator. For site to patient delivery, the site performs a dispensing visit as per normal practice, but the distribution vendor or specialist courier is contacted to pick up the materials and deliver to the patient. In either case, the distribution network must make arrangements directly with the patient for the delivery of the materials and establish a chain of custody with documentation and signed acknowledgement of receipt of the materials by the patient.

Additionally, it will be necessary to undertake a risk assessment of the distribution network to identify required procedures including those that may be necessary, dependent on the mode of delivery, to prevent un-blinding, document product stability as well as verifying that the materials have arrived in good condition prior to release of the materials to the patient. Finally, documentation for the investigator and sponsor must be provided. In the case of documentation to the sponsor, all patient identity information must be removed to be in compliance with data protection regulations.

Reverse engineering of the supply chain for used or expired patient materials also should be considered. In these cases, the same chain of custody requirements are applied from the pick-up of the materials from the patient to the site of destruction either at a depot or at the site. If destruction occurs at a depot, the site should be provided with all accountability documentation.

Appendix 1 provides some outline guidance on the types of study criteria that may benefit from a DTP strategy.

Some frequently asked questions around the management and practicalities for employing a DTP strategy include:

Overall, how is the supply chain organized to keep control?

The supply chain needs to be clearly laid out and documented before submission to the regulatory bodies as this will be one of their main areas of focus during their review. It is particularly important to show how any recall procedures would operate, how the patient is able to be supplied the materials in a timely manner, and how patient compliance

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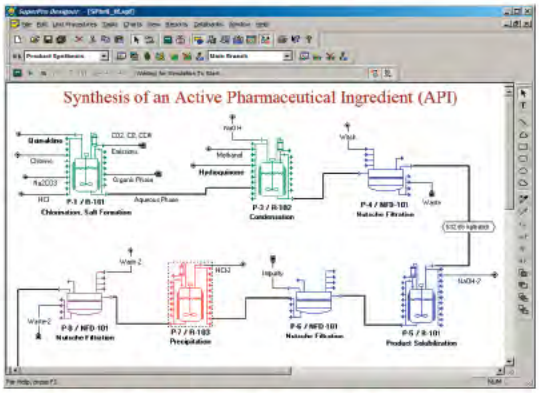

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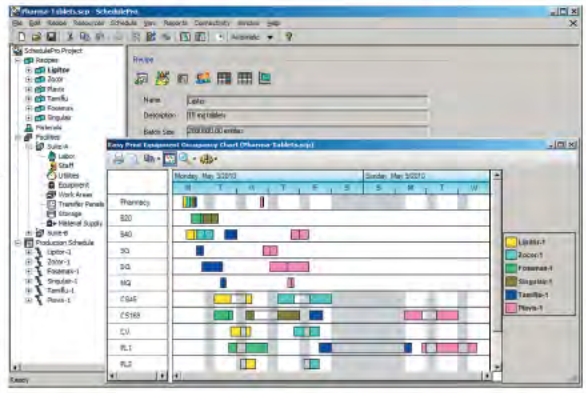

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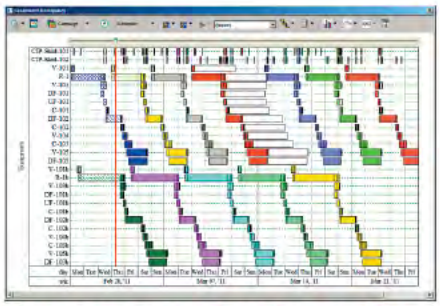

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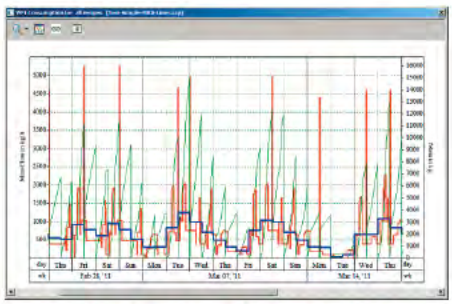
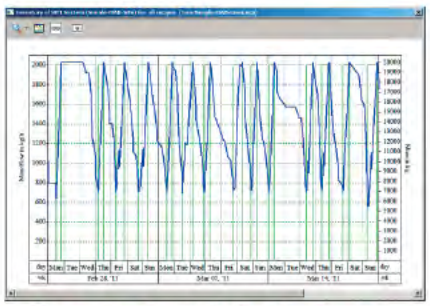


Tracking demand for resources (e.g., labor, materials, utilities, etc.)



Managing inventories for input, intermediate, and output materials

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can be assured. Sponsor, depot and sites will need to be very clear on their documentation control as they will be open to inspection from the local regulators, this can cross all variants of GxP.

Who can ship? What type of courier?

A key part of the DTP distribution network/supply chain may need to be delegated to a courier; this is an important aspect to the success and compliance of the trial. It also may be possible to co-operate/coordinate with a home nursing/care network. A clear contract and Quality Agreement should be in place with the courier, or the Clinical Research Organization (CRO) that is managing them on your behalf. Specific training also will be required for the courier involved. If a courier is involved, they should not enter the patient's residence or initiate any dialogue around the study or signs and symptoms, but depending on the requirements of the protocol, this training could involve waiting for the named patient to be present to receive the supplies and/or taking the data logger and excess packaging back to the depot. There is also the potential for additional interaction requirements within the Interactive Response Technology (IRT) system in use for the protocol.

It is critical that the courier company involved operates to GxP standards and has a level of compliance that at the very minimum will meet Good Distribution Practice (GDP) requirements for all aspects of the shipment. This includes assurance that all related documentation is provided to the appropriate Trial Master File. The courier company needs to have a well-designed and clear set of SOPs in place, which also describe contingency plans, e.g., what happens when they cannot deliver to a patient if there is a temperature excursion in transit to the patient and whether it is acceptable to deliver to anyone but the patient. The courier company also would need to ensure compliance with local laws and regulations (e.g., obtaining and maintaining the appropriate permits and licenses if required) to provide such a service.

Typical Criteria that support the benefits of a DTP Strategy
Study Trial duration is over 2 years
Robust stability profile of IMP
Distribution Chain is located in each country of operation
Distribution Chain is trainable on GMP/GCP
Patient visit windows are > 3 months
Trial employs dispensing only visits (no medical check)
Trials employs home administration by study nurse
Patient to site ratio is less than 3:1
Patient population is remote from clinical sites
Patient transport of IMP is burdensome (e.g. large amounts, temperature sensitive)
Ethics Committees/local regulations are open to direct to patient

Appendix 1.

Is it ever appropriate to post clinical supplies to patients?

In the UK, Royal Pharmaceutical Society of Great Britain (RPSGB) has provided guidance on when delivery and posting of medicines to patients is appropriate.[8] Risk assessment by the clinical site is required and many hospital pharmacies may derive mitigation strategies which review packaging requirements, safe use of the medicine by the patient in addition to supporting the use of mail services that have acknowledgment of receipt as well as processes that ensure appropriate return of undelivered packages. Typically, these mailing mechanisms would be utilized only in the case of highly stable non-controlled (non-scheduled) or non-hazardous IMPs.

Shipment Request Process

The shipment request regardless of distribution route in many cases will be generated by the IRT system, and thus dispensing is generated by a "visit" recorded by the Principal Investigator (PI) and subsequent information being uploaded into the IRT system. Any level of manual oversight is dependent on the sponsor company, protocol design and system requirements. The important elements that must be captured is PI assessment of the patient and their assignment of the IMP to the patient, assurance that the IMP has been stored appropriately and has valid 'use by date/expiry date' and that in general, IMP is not dispatched unless all specifications of the protocol have been met.

What requirements are there at the patient end?

Training of the patient in these protocols also has an important significance. They need to know what to expect when the courier meets them, including formal identification, etc. In addition, the patient needs to know what they should do with the package and what they have to provide back to the courier. They need to be taught how to physically receive the supplies and in some cases depending on the set-up, they may be required to report information to the PI either through an IRT system or other mechanism. Given the burden of compliance on the patient, the trial design that accommodates DTP might be limited.

Returns and Reconciliation Process

As indicated earlier, ideally the supply chain should be reverse engineered to enable the returns to be collected by, where used, the courier company in the same way that the

deliveries are made (pre-calling and other arrangements). Once this has been done, the returns should be taken to a central location and there the reconciliation can be undertaken to the appropriate standard deemed by the protocol. The central location could be a CRO/CMO, courier company depot, the main investigating site or the sponsors own facility, but this should be a clear part of the supply chain design prior to the study start.

Implications for the Clinical Site

It must be very clear to the clinical site involved what their role in DTP is and what the expectations are for them in the management of the IMP. As this is not a normal process, they will need to have appropriate training and it is good practice to provide a clear diagram/process flow to show what they are expected to do and how this works with the patients and supply chain activities as well as timings and responsibilities.

Management of Interactions with IRT Systems

The IRT system, if well designed for the protocol, could be helpful in enabling a real-time picture of the status and location of the supplies. However, a poorly designed set-up could adversely affect the logistics of the protocol. It is necessary to define how reordering limits should be set-up in the system, who is going to acknowledge receipt of the materials at the patients home address, as well as more fundamental questions including should central facilities be shown in order to manage the levels of inventory.

Conclusion and Summary

There is a growing need from sponsors and clinical sites as well as a desire from the patient population for clinical supplies to be shipped direct to patient homes. The regulatory environment is changing, but as yet for many countries, this is "uncharted territory" although the rules of GCP for the most part prevail.

Options and frameworks do exist to support this strategy; risk assessment and early dialogue with the regulatory authorities/MOH being the key to success. This article presents and outlines our understanding of this capability at the current time; however, with increasing end user demand and industry experience, an updated and more detailed overview may be provided in the years to come.

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Adrian Peskett has worked at Pfizer for 12 years, initially establishing a Global Clinical Supply Chain. The role included working on global and site processes and standards, as well as the development of demand planning tools across all contributing functions. For a year he then worked to establish an Asian Pharmaceutical Sciences business strategy for Pfizer. In 2008, he began working with the Clinical Supply Logistics group and was involved in implementing the global distribution strategy, including management of Vendors, mapping and implementing the depot network and helping to establish a global brokerage. Since the beginning of 2014 he has been working in a new group that is establishing a new process around the management of Comparators globally for Clinical Trials.

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Isolators Selection, Design, Decontamination, and Validation

by Nick Barbu and Robert Zwick

This article presents the selection, design, and validation of isolators to be used by the Musculoskeletal Transplant Foundation for the production of Demineralized Bone Matrix putty.

MTF is a supplier of Allograft – bone and dermal tissue. The purpose of this isolator project involves the production of Demineralized Bone Matrix (DBX) putty. DBX putty is processed human bone that has been demineralized and combined with sodium hyaluronate (HY), which is a naturally derived material not of animal origin that is both biocompatible and biodegradable. The combination of demineralized bone and sodium hyaluronate results in a putty-like consistency for ease and flexibility of use during surgical application. DBX putty is intended for use as a demineralized bone matrix for voids or gaps that are not intrinsic to the stability of the bony structure. DBX putty is indicated for treatment of surgically created osseous defects or osseous defects created from traumatic injury. DBX putty can be used as follows:

- Extremities
- Posterolateral spine
- Pelvis
- Ridge augmentation
- Filling of extraction sites
- Cranium
- Craniofacial augmentation
- Mandibular reconstruction
- Repair of traumatic defects of the alveolar ridge, excluding maxillary and mandibular fracture
- Filling resection defects in benign cysts, or other osseous defects in the alveolar ridge wall
- Filling of cystic defect
- Filling of lesions or periodontal origin
- Filling of defects of endodontic origin

DBX putty is packaged in a glass syringe and must be extruded into a sterile basin and is not injected directly into the operative site. DBX putty can be used alone or mixed with autogenous or allograft bone or with bone marrow aspirate. Since the DBX putty is introduced into the body, it must be produced and packaged under aseptic conditions and procedures. Aseptic process refers to the condition of being free from all forms of life, including bacteria, fungi, and viruses. Aseptic technique refers to efforts to maintain a sterile field during a procedure to prevent infection. These efforts include utilizing sterilized instruments and supplies and requiring staff to wear sterile gloves and other clothing, such as caps, gowns, and masks to reduce potential contamination.

The process whether conducted in either a cleanroom, biological safety cabinet, or an isolator is largely the same with the exception of the decontamination cycle. In order to maintain the highest aseptic techniques, it was decided to move the DBX putty process to isolators for their ease of use in cleaning and decontamination.

Barrier isolation technology has been recognized by the Food and Drug Administration (FDA) for a number of years as an effective method of aseptic processing. The DBX mix-fill, measuring and packaging processes were all set to be performed in isolators, decreasing the likelihood of microbial contamination. Isolators also have the added benefit of increased personal safety and comfort for the processing technicians.

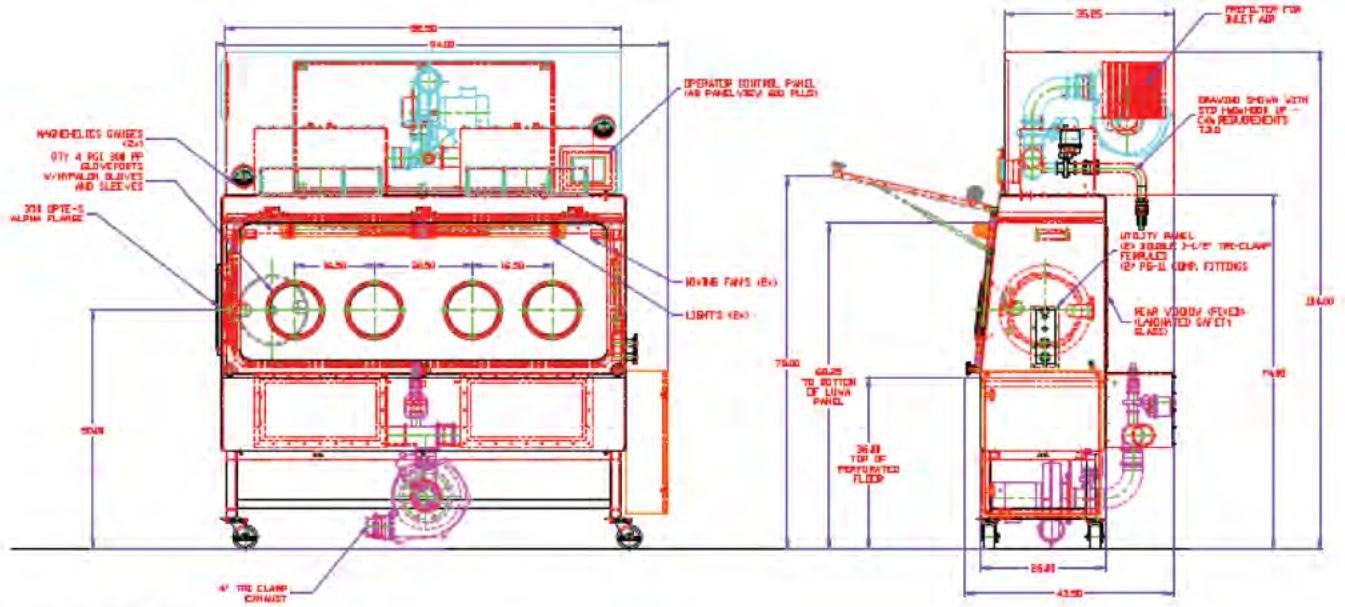

Figure 1. Mix/fill isolator.

Isolator Selection

Isolators technology selection was an important step in the process design with many factors. What size should the isolator be? What equipment should be inside the isolator? Which isolator manufacturer should be selected? After considerable research and discussion an isolator supplier was chosen. The production process was broken down to two isolators: 1. the mix fill isolator for mixing and filling and 2. the packaging isolator where final product packaging is performed. Both the mix fill and packaging isolators are about 100 cu ft (2.8 cu m) each. The packaging isolator was designed to hold the packaging equipment which added a sealer compartment to its layout. The packaging isolator also required the ability to decontaminate and transfer materials in and out of the main chamber which added an air lock to its layout. See Figures 1 and 2.

Decontamination Method Selection

Once the isolator was chosen, the decontamination method was selected. In order for this process to be economically

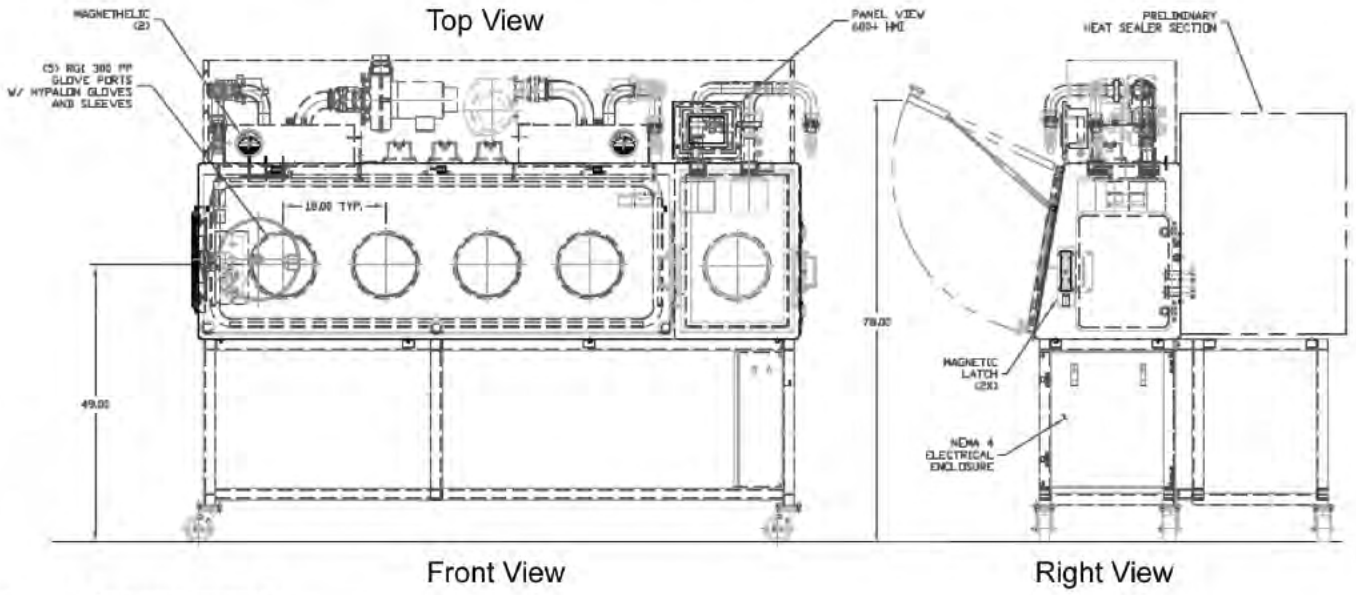

Figure 2. Packaging isolator.

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The Musculoskeletal Transplant Foundation (MTF) is the nation's leading tissue bank. One of the ways MTF is raising the standards of production to higher levels has been by investigating, designing, selecting, and validating the use of isolators in the production of Demineralized Bone Matrix (DBX) putty. To accomplish this, the authors had to understand isolation technology and identify the requirements of production, decontamination, and overall validation. Isolators were used in conjunction with chlorine dioxide gas decontamination, working together to provide a simple systems integration. Both products met the needs of MTF for ease of use, design, flexibility, decontamination cycle effectiveness, and time.

feasible, the decontamination process had to take less than two hours. If the sterilization/decontamination time exceeded two hours, the product would not be cost effective enough to warrant the change from cleanroom processing to isolation processing. The choice for sterilization/decontamination method was between vapor phase hydrogen peroxide and chlorine dioxide gas. Both methods were known to be effective, as both are registered with the US-EPA as sterilants. Similarly, Vapor Phase Hydrogen Peroxide (VPHP) and Chlorine Dioxide (CD) gas have both been used in cleanroom environments and in isolators.

VPHP has been around a long time, as it was developed in the late 1970s.[17] It has benefits when used for sterilization, such as it does not leave residues. The vapor is generated by boiling or vaporizing a solution of hydrogen peroxide, typically 35% hydrogen peroxide/65% water. This vapor is then injected into the target chamber. The VPHP process will have varying amounts of condensation since VPHP is not a true gas at room temperatures (hydrogen peroxide boiling point 109°C). The condensation amount is minimized or maximized depending upon whether a high or low RH system is utilized. Another issue with VPHP is a potential for poor distribution[9,21] and penetration abilities into 5 mm gaps[23] and small tubing and openings.[3] The potential for reduced distribution was of particular concern to MTF due to the complex surface geometry of the sealer used in its packaging isolator. For these reasons, MTF also looked at chlorine dioxide gas as a decontamination method.

Chlorine Dioxide (CD) has been used in many applications, such as studies and research,[11,8] isolators,[1,4] processing vessels,[5] HEPA housings with small tubing,[3] BSC's (NSF Standard 49, 2008)[15], rooms,[13,20] and large facilities.[2,14] It is a gas at room temperatures (boiling point 11°C) and is not considered to be carcinogen by IARC, NTP, OSHA, and ACGIH. CD gas does not leave a residue. As a true gas, complex surface geometry is not a factor as the gas will achieve complete, natural distribution of the space it is contained within. Chlorine dioxide has shown promising results with organic loads, including studies at Public Health Agency of Canada showing kill with organic soiled loads,[12] wood, carpet and ceiling tiles,[18] under mouse cage bedding,[22] and HEPA filters loaded with soil.[15]

Chlorine dioxide gas was chosen as the sterilant due to its fast cycle times and evidence of its effectiveness. With the reduced cycle times, MTF's decision to move forward with isolators became feasible. MTF's requirement was to demonstrate a complete kill of 6-log biological indicators with a total cycle time of less than two hours including chamber leak test and aeration. To accomplish this, the Cloridox-GMP chlorine dioxide gas generator was chosen as seen in Figure 3.

An early feasibility study using chlorine dioxide was conducted to test potential concerns about product viability, due to any residual left after decontamination. Tests involved exposing the demineralized bone to concentrations of 5 mg/L for 30 minutes (extreme test) and the demineralized bone and sodium hyaluronate to 0.1 mg/L for 45 minutes to test the maximum residual ClO_2 concentration after aeration. The results of these tests gave confidence that aeration down to 0.1 ppm of residual ClO_2 (the Permissible Exposure Limit (PEL)) would not affect the efficacy of their final product. The materials were processed into DBX putty and tested for osteoinductivity, pH, penetration, and irrigation. The test results for all samples fell within the requirements for DBX putty.

Residual tests were performed by outside testing laboratories, on final product which had been exposed to post aeration levels of residual ClO_2 (0.1 ppm). A method similar to EPA 300.1 and 326.0 using ion chromatography was used to measure oxyhalide disinfection (ClO_2) by-products in an extract of DBX putty. The limit of detection was determined

Figure 3. Cloridox-GMP and mix fill isolator.

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to be 3 ppm, all samples tested below the limit of detection. This gave confidence that if any residual CD gas was left inside the isolator it would be significantly lower than the allowable levels.

Once chlorine dioxide gas was chosen as the decontamination method, the cycles needed to be developed (decontamination Performance Qualification (PQ)). Chlorine dioxide gas cycles are similar to ethylene oxide such that humidity needs to be added before the gas is introduced. Raising humidity in the isolator is a simple process using a very small commercially available steam generator. The steam generator is filled with Water for Injection (WFI) and a heater heats the water to produce the steam. The Cloridox-GMP has an Relative Humidity (RH) probe which measures the RH in real time and turns on the steamer to add RH if it is below the set point. A decontamination cycle for chlorine dioxide contains 5 steps: 1. Precondition, 2. Condition, 3. Charge, 4. Exposure. and 5. Aeration. The precondition step includes two functions: leak testing the isolator and raising the RH to the desired set point. The isolator performs the leak test, which if successful, releases the interlock allowing the Cloridox-GMP to start the cycle by raising the humidity to the set point of 65%. Once the RH is at 65%, the cycle advances to the condition step, where the RH is maintained for 10 minutes. After condition, the cycle advances to the charge step where the chlorine dioxide gas is introduced to the isolator to reach a concentration of 5 mg/L. The chlorine dioxide gas is generated by the following equation: $Cl2_{(g)}$ + $2NaClO2_{(s)}$ = $2ClO2_{(g)}$ + $2NaCl_{(s)}$. In this process, chlorine gas is passed through solid sodium chlorite cartridges and a pure chlorine dioxide gas is produced with no byproducts introduced into the isolator. The sodium chloride byproduct kept inside the cartridges. When the concentration is verified by the real-time concentration monitor to have met process set point, the cycle advances to the exposure step where the concentration is maintained for 50 minutes. If at any point during the cycle the CD concentration drops below the set point, the Cloridox-GMP automatically stops the exposure timer and adds more CD, when the required concentration is restored the exposure timer is restated. So, if the concentration falls below the set point at any time during the exposure, that time is not accumulated in the exposure time. For example, if the exposure time is 30 minutes and the concentration falls below set point for one minute, the overall exposure time will be 31 minutes. This guarantees an exposure at the desired concentration for the desired length of time, thereby ensuring all cycles are efficacious each and every time. The CD concentration is monitored by a photometer which outputs an absorbance value, which corresponds to a concentration of chlorine dioxide measured in mg per liter. Once the exposure time is completed, the aeration or gas removal step starts. During aeration, CD gas is removed from the chamber by allowing clean air into the chamber and removing CD to an outside exhaust. When gases are removed from chambers, typically half the gas molecules are removed with each air exchange. For example, a 100 ft^3 (2.8 m^3) isolator with 5mg/L CD gas concentration and a 50 cfm exhaust (85 cu m/hr) rate, would need approximately 24 minutes, or roughly 15 air exchanges, to bring the CD concentration in the chamber to 0.1 ppm or below. The 0.1ppm (0.3 milligrams per cubic meter (mg/m(3)) concentration level is the eight hour Time Weighted Average (TWA) for the Permissible Exposure Limit (PEL) of chlorine dioxide.

Validation

Validation is a time consuming endeavor for new products, processes, or new equipment. For this case study, it was both a new process (moving to isolators) and new equipment (new isolators and decontamination equipment). The process used to validate the new equipment and process is as follows:

1. Factory Acceptance Testing (FAT) of isolators
2. FAT chlorine dioxide generator
3. Site Acceptance Testing (SAT)/commissioning of isolators
4. Installation Operational Qualification (IOQ) of isolators
5. Performance qualification/decontamination cycle development
6. Process qualification, unique to process being performed in the isolator/s
7. Validation, media fill/aseptic fill, again unique to process preformed in isolators
8. Risk assessment

1. Factory Acceptance Testing (FAT) of Isolators

This step was essentially an IOQ light conducted at the manufacturer's location. The key points for successful isolators FAT were identified prior to the trip. The key tests were a successful leak test. For this test, the isolator was pressurized and monitored for pressure decay over time. The pressure set point was 1.5" of water column with an allowable drop of 0.2" of water. After the pressure decay test, a smoke test was completed. This demonstrated air flow through the isolator chamber. This was particularly important for processes requiring either laminar flow or low particle counts. Finally, a functional verification of all equipment and operator interfaces, check lights, valves, blowers, etc., work in the appropriate operating mode (Decon, Production, Stand By, etc.)

2. FAT Testing for Decontamination System

The FAT for the decontamination testing was done at the manufacturer's facility with the generator to be purchased. A cycle was tested on a small 17 cu ft isolator supplied by the decontamination equipment manufacturer. A few biologi-

cal indicators were placed inside the isolator and a cycle was run. The cycle that was run had process parameters of 65% RH for 30 minutes of conditioning and 5 mg/L concentration of chlorine dioxide gas for an exposure time of 30 minutes. After the exposure, the BIs were incubated for seven days and checked for growth. No growth was observed. In addition to the efficacy testing, a few alarm functions were tested along with consumable change out. All functions tested performed as required. Additionally, the manufacturer of the decontamination equipment performed and documented a complete FAT which tested the proper wiring and cycle functions to ensure the equipment functions according to specifications.

3. Site Acceptance Testing (SAT)

Upon equipment arrival, SAT/commissioning tests were performed. With the exception of verifying the communication between the CD generator and the isolators, these tests were similar to the FAT with more of an emphasis on making sure everything arrived in working order and functioned according to the manufacturer's tests. Both the FAT and SAT are not generally a part of MTF's validation package and were performed primarily to get a feel for whether or not the equipment, people, and process were ready for validation.

4. Installation Operational Qualification (IOQ)of the Isolators

The first step of performing the IOQ was to ID or document the isolator equipment. Each major component was identified along with supporting documentation. The supporting documents are such things as calibration sheets, filter certifications, operational manuals, system drawings, and standard operating procedures. A few examples of major components to verify would be HEPA filters, power supplies, motors, sensors, valves, and most other parts with a model/serial number on them. After supporting documentation and major components are identified and recorded, software versions are then verified to be correct and current.

The next step is the Operational Qualification (OQ). In this step, the equipment functions or modes are verified. Some of the functional tests conducted were power failure and recovery (does the isolator power up and recover from power loss in the right mode?), pressure control (does the isolator maintain the positive pressure that was required?), pressure alarms (does the isolator alarm if pressure drops or spikes?), automated leak test verification, particle count verification, airflow verification (using smoke to verify airflow and the airflow velocity was measured) and lastly the RTP port and beta container were verified to connect and disconnect.

After the isolator was verified to function, the IOQ of the chlorine dioxide gas generator was started. The steps performed here were similar to the isolator IOQ such that the critical equipment was documented along with verification of the equipment and the supporting documentation: calibration certifications, manuals, and drawings. After the documentation was compiled, the software versions were noted. After the IQ was completed the OQ was conducted by loading consumables, alarm testing of key alarms, testing of communication between the isolator and the chlorine dioxide gas generator, power failure recovery and finally cycle verification.

5. Performance Qualification Decontamination Cycle Development

Once all users were trained on the chlorine dioxide gas generator and the training process was documented, the cycle development for the decontamination cycle could begin. This was started by determining a D-value for the biological indicators (fractional negative method used by Stumbo, Murphy and Cochran) and enumerating the BIs to verify the population with the manufacturer's specification. After the D-value and enumeration, the decontamination cycle development began. BIs were placed at various locations within the isolator chambers as seen Figure 4 and 5.

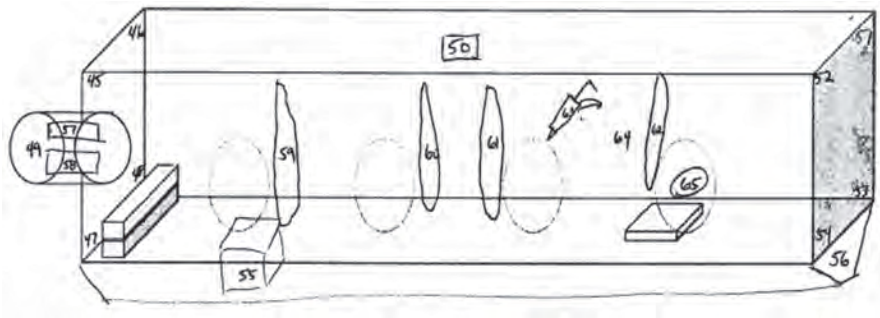

Figure 4. Mix fill isolator BI locations.

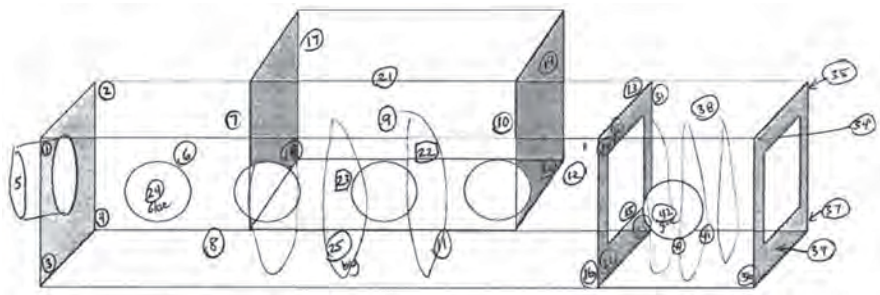

Figure 5. Packaging isolator BI locations.

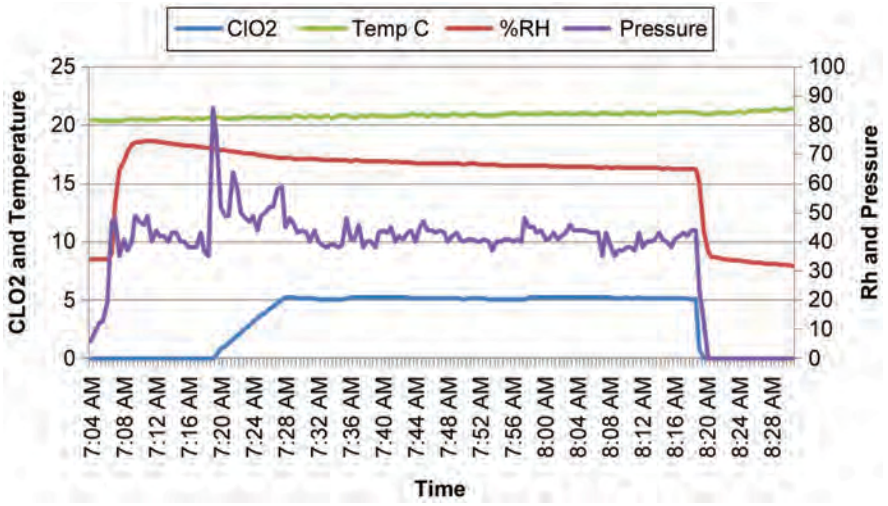

Figure 6. Mix fill isolator decontamination cycle chart.

After BIs were placed, cycle development started with the suggested cycles of 65% RH for 30 minutes of condition time followed by charging to 5 mg/L (1800 ppm) and holding for 30 minutes of exposure. After testing a few other cycle times, the cycle that was finally used was 65% RH for 10 minutes of condition time and 5 mg/L for 50 minutes for a total cycle time of fewer than 90 minutes. Even though both isolators were different configurations (layout), the same cycle proved to be optimum for both isolators.

Once the cycle had been developed, it needed to be verified with a minimum of three consecutively successful runs demonstrating a complete kill of all BIs. An important note here is that this does not demonstrate an SAL for the isolator system. Since BIs with more than a million (10^6) bacterial spores were used, our answer to the sterility assurance question is, "Has demonstrated a complete kill of 10^6 Biological Indicators" The cycles were tested using 10^6 *bacillus atrophaeus* (ATCC 9372) Biological Indicator (BI) spore strips inoculated on paper and wrapped in tyvek. BIs were placed in 25 (packaging main chamber) 13 (air lock) and 21 (mix/fill) locations around each isolator, see Figures 4 and 5 for locations. Figure 6 shows a chart of the decontamination cycle in the mix fill isolator. It documents the RH monitoring and control and the concentration monitoring and control in real time. It also shows a cycle under the two hour requirement. The actual cycle time is 85 minutes.

6. Process Qualification, Unique to the Process Preformed in the Isolators

The most problematic portion of this validation was to maintain the appropriate non-viable particle counts. The mix/fill process involves mixing a dry powder and a gelled liquid in an ISO Class 4 isolator with less than or equal to 354, 0.5 and 0, 5 micron particles/M^3. This was largely accomplished by good aseptic technique, sample averaging and closely defining critical processing steps. Critical processing steps for mix/fill have been defined as the time that tissue is exposed to the isolator chamber.

7. Validation, Media Fill/Aseptic Fill, Again Unique to Process Preformed in Isolators

The media fill validation is simply running the process with a microbial growth media in place of our bone powder and HY then incubating the resulting packaged simulated product. Because the DBX putty is not a liquid, a custom media needed to be developed using both a sterile powder (TSB and CMC) and a liquid, (Water for Injection (WFI)) to create a reasonably translucent and viscous gel. Once developed, the media was validated to demonstrate growth promotion. All test samples demonstrated no growth.

8. Risk Assessment

The risk assessment was conducted using an ISO 14971 style assessment of the risks to patient/tissue. Using a team of experts familiar with the DBX putty process conducted in Biological Safety Cabinets (BSC) and a consultant familiar with aseptic processing in isolators, a Failure Modes and Effects Analysis (FMEA) work sheet was used to identify the potential failure modes, potential effects of failure, severity, potential causes of failure, occurrence, current controls and detection. Severity, occurrence and detection were each rated on a scale of 1 to 5 for each potential effect listed by the team. The product of the severity, occurrence and detection ratings is called a Risk Priority Number (RPN) which is used to rate the overall risk associated with each potential effect of failure. Generally higher RPNs require more/better controls.

All tissue, HY and packaging materials are packaged in sealed pouches which have been validated to prevent sterilant intrusion. Additionally, after the decontamination cycle the isolator chamber is aerated to less than the current eight hour permissible exposure limit (0.1 ppm), before any processing materials are exposed to the isolator chamber. In addition to the above, a CD residuals study was conducted on DBX putty which had been fully processed in the isolators. This study determined that there was no detectable level of CD in the DBX putty. This level of control results in an easily acceptable level of risk to both product and patent.

Discussion – Lessons Learned

Some lessons learned from the process include checking

materials used inside the isolators and the material of the isolator itself. Chlorine dioxide gas is an oxidizer. Its oxidation potential is 0.95.[24] Some materials chosen for equipment inside were incompatible with the number of cycles performed daily (two to three cycles per day). A few of the unpainted mild steel components in the heat sealer suffered some oxidation leading to progressively higher nonviable particle counts. This corrosion was initially fairly subtle, and once we had run enough cycles to cause more visible corrosion, it became apparent that not only the materials, but the surface finish of the materials were critical to achieving low nonviable particle counts; for example, the cold rolled steel shafts in the sealer have remained unaffected by exposure to chlorine dioxide except where slots and flats have been milled in them. Basically uncoated ferrous metals required paint or another coating; however, the aluminum extrusions used for the sealer have remained unaffected by chlorine dioxide exposure. Once we discovered what was going on, the affected parts were changed to more compatible materials (stainless steel and some plastics), or coated, the air exchanges were increased and the particle counts were reduced to acceptable levels.

Another issue we discovered was that not only the volume of air going through the isolator is critical, but the direction as well. Our mix fill isolator brings air in from the top and extracts air through the floor and out the back of the bottom.

Some lessons learned from the process include checking materials used inside the isolators and the material of the isolator itself.”

This looked like a good way to extract particles as quickly as possible during the mixing operation. Unfortunately, this also requires that the floor of the isolator be kept clear to allow the air to flow through it. Since all the materials and equipment are locked in the isolator from start to finish, material location and work flow not only need to focus on efficiency of the process, but air flow through the isolator. We were able to overcome these limitations with improved work flow, strict attention to aseptic technique, and a trash basket built into the floor of the isolator.

Conclusion

MTF decided it needed to raise the standard of production to ensure product safety by processing and packaging its DBX putty inside isolators. Because of this a company wide effort to investigate isolators, choose the manufacturer, select a decontamination method, and validate the isolators and decontamination agent, and finally manufacturer product through the new process. It decided upon isolators used in conjunction with chlorine dioxide gas decontamination. The isolators eliminated the need for using 2.5 ISO 4 cleanrooms and provided true aseptic processing. The chlorine dioxide gas generator and isolators worked together to provide a simple and seamless systems integration. Both products met the needs for ease of use, design, flexibility, and decontamination cycle effectiveness and time.

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Ease Your Reshoring Transition with the Right Domestic Outsourcing Partner

by Mark Danna

This article presents an overview of current reshoring trend, some of the factors fueling that trend, and a discussion of how the challenges of reshoring can be ameliorated by teaming with a domestic outsource partner.

An increasing number of companies are considering reshoring manufacturing to the U.S. Employing the right domestic outsource partner can minimize the pain and costs of such activities.

After nearly a quarter of a century, the off-shoring manufacturing trend that decimated the U.S. manufacturing sector and played a significant role in the slow pace of the current economic recovery is beginning to end. While this reshoring trend might be considered a ripple rather than a wave in the economic waters, it is growing. According to a study conducted in August 2013 by the Boston Consulting Group (BCG), 54 percent of the more than 200 companies surveyed were planning or seriously considering reshoring some of their manufacturing. That is a 17 percent increase over the 37 percent considering reshoring in 2012 when BCG last conducted the survey. Twenty-one percent of respondents said they were actively engaged in reshoring or will do so in the next two years, double the number reporting such activity a year ago as seen in Figure 1.

According to Harry Moser, former CEO of Charmilles Technology Corp. and founder of the Reshoring Initiative, more than 50,000 manufacturing jobs returned to the U.S. between 2009 and 2012. In the five years previous, the number returning was close to zero. Those 50,000 jobs constitute about 10 percent of the new manufacturing jobs created in the U.S. over the last three years.

The majority of the returning manufacturers so far, such as NCR, Apple, Google, Caterpillar, Whirlpool, and Ford, all represent traditional manufacturing sectors. However, the

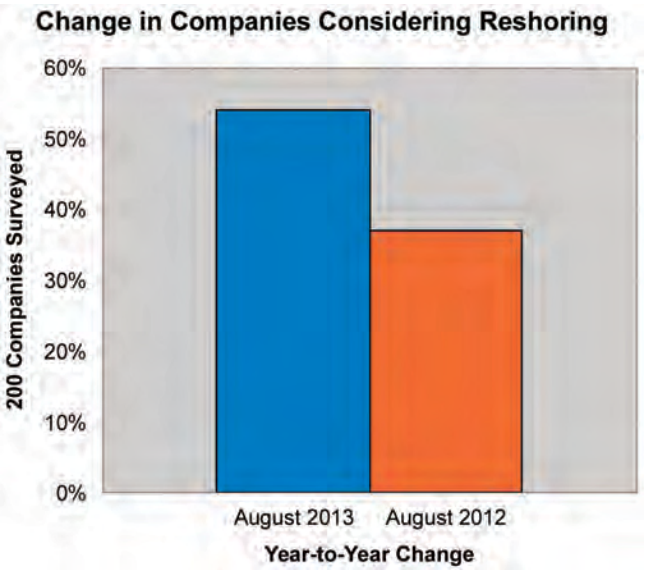

Figure 1. According to a survey conducted in 2013 by the Boston Consulting Group, 54 percent of 200 companies surveyed were considering reshoring as compared to the 37 percent who were considering it in 2012.

same factors that have caused these companies to reshore also impacted those biotechnology firms that have offshored in the last decade. It's time for biotech companies, if they are not doing so already, to consider the benefits of reshoring.

Contributing Factors to the Reshoring Trend

There are a number of factors that are causing many American companies to consider moving their manufacturing operations back home. While the two most significant are wages and productivity, there are a number of others, including a culture of innovation, access to venture or government funding, product quality and protection of IP, that should be of particular concern for companies in the pharmaceutical and medical device industries.

Let's look first at wages and productivity. According to an April 2013 Bloomberg article, the average pay in Asia almost doubled between 2000 and 2011. During that same period, wages increased by only 5 percent in the developed world and 23 percent worldwide. This dramatic wage inflation seriously erodes what was considered a prime benefit of offshoring.

When this upward wage trend is coupled with differences in the levels of productivity of American and foreign workers, reshoring becomes even more attractive. According to an International Labor Organization (ILO) report, American workers out-produced and worked longer hours than their counterparts in Japan, Switzerland, and all 27 EU countries. While it is true that workers in Asia tend to work longer than do American workers, this is also changing. Chinese workers, for example, have recently been demanding shorter hours and even job tenure after a certain number of years on the job.

Interestingly, although they spend fewer hours on the job, American workers consistently out-produce their Chinese counterparts. According to ILO statistics, the average Chinese industrial worker produces $12,642 worth of output per year, while the average Chinese farmer or fisherman produces about $910 worth of output in the same time. By comparison, an American worker in the industrial sector produced $104,606 worth of output and a worker in the farming or fishing sector produced $52,585 per annum as seen in Figure 2.

When one considers the diminishing difference in labor costs and the magnitude of difference in worker productivity, reshoring starts to become a very attractive alternative. It becomes even more attractive if one considers some additional factors.

Logistics are vastly simplified. Parts and finished goods will generally be shipped shorter distances, saving both time and cost. The expenses and risks in maintaining a global supply chain are significantly reduced. In a world where geopolitical tensions are rising, especially in Asia, the risk to a company's global supply chain should be of increasing concern. As an additional benefit, communication across multiple time zones is also minimized.

Reshoring and the Biotech Industry

Additional issues, such as quality, protection of IP and political stability should be of particular interest to biotech companies. As China engages in increasingly tense confrontations with her neighbors over disputed territories, the likelihood of confrontations with the U.S. grows accordingly. Such confrontations could seriously impact any U.S. company engaged in manufacturing operations in China – working with Chinese Contract Research Organizations (CROs), for example.

The use of offshore CROs – initially seen as one of the benefits of offshoring – has had some unintended consequences in terms of increased competition. While there have been unsubstantiated concerns about theft of intellectual property, CROs in China and India have begun developing and marketing their own drugs in the developing world, and in some cases in the U.S. and Europe. These companies have not stolen IP, what they have done is gain valuable insight into the successful business practices of large U.S. biotech companies. Offshoring has essentially created the undesirable situation in which competitors are also key service providers.

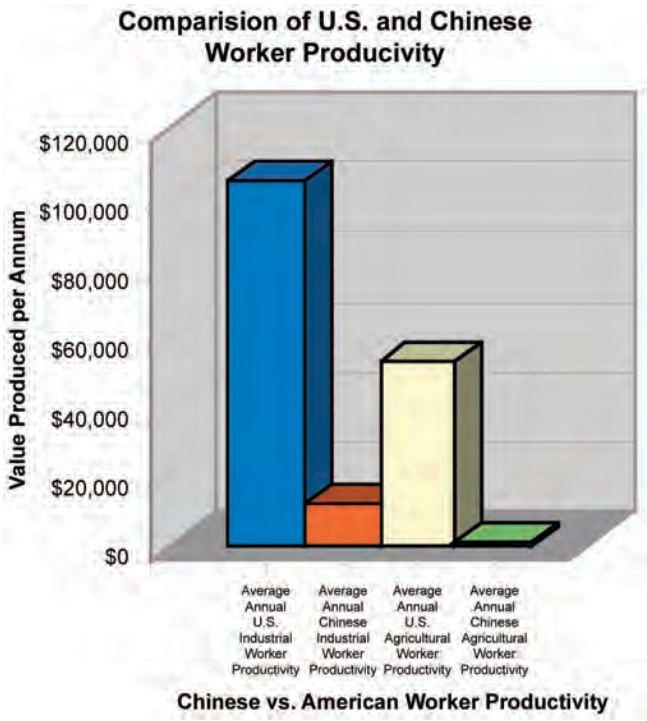

Figure 2. According to recent statistics from the International Labor Organization, American industrial and agricultural workers significantly out produce their Chinese counterparts.

Quality control is another realm where reshoring provides benefits to biotech firms. While the general business community in the U.S. frequently complains about over-regulation, biotechnology is an area where the stringent regulations directly contribute to adherence to best scientific practices, thus helping to ensure both the quality and reliability of both basic scientific research and product manufacturing.

Interestingly, according to a 2011 California Biomedical Industry Report, published by the California Healthcare Institute, the CEOs of many of the biotech firms located in California intended to increase jobs (68 percent), manufacturing (41 percent), and R&D operations (62 percent) in the state. This despite the frequent complaints heard about California's excessive regulations and the cost of doing business in the state. The main reasons cited for expansion of operations in California included availability of a highly skilled entrepreneurial workforce, the state's culture of innovation, and access to leading research universities. While focused on companies already located in the U.S., this report highlights the benefits biotech companies gain from locating in the U.S.

Reshoring Challenges

Of course, a decision to move a company's manufacturing back to the U.S. offers its own set of challenges. Building a manufacturing facility and training workers can easily take a couple of years and a considerable investment in capital. In the meantime, customer demand must still be met.

Once a company decides to reshore, it has to handle the logistics of closing its overseas facility, transferring the technology, and validating the manufacturing process, as well as obtaining regulatory audits and approval for the new facility. It also may require dealing with overseas employees and a host country that are less than supportive of its reshoring decision. An American factory manager in China, for example, was briefly held hostage by his factory workers over rumors the company planned to move its manufacturing back to the U.S.

It is critical to consider your customers in your reshoring equation. It's vitally important to assure them that your reshoring transition will not interrupt their expected flow of finished products or lead to significant increases in their price.

Easing the Reshoring Transition with Domestic Outsourcing

Ironically, the solution to these challenges can be found in outsourcing – but domestic rather than overseas outsourcing. A domestic outsourcing partner can provide the engineering and manufacturing resources that are needed to minimize the pain involved reshoring.

Partnering with a domestic design house for manufacturing equipment solutions offers significant advantages. The outsource partner will have a core of experienced engineering design teams used to bringing multiple new designs to volume production every year. In addition, most will have access to established U.S. manufacturing facilities capable of producing products in volume. As a result, whether bringing an established production line back to the U.S. or building a new one, collaboration with the right outsourcing partner can make the reshoring transition seamless from a customer's point of view. Of course, the key is picking the right outsource partner.

Picking the Right Outsourcing Partner

The very first things to consider when deciding to choose a domestic outsource partner to smooth your company's reshoring transition is their size, technical expertise and regulatory experience. Do they have the resources to provide the engineering support you need? Do they have so many clients that your project won't receive the attention and support it needs to succeed? Most importantly, do they have experience in your industry or one that is closely related? An outsourcing company with significant design and manufacturing expertise for custom production equipment may be an excellent partner for food production, cosmetics and nutritional supplement industries, but may not be the best choice for a company producing regulated drug products, biologics, medical devices or diagnostic products.

Once having found a domestic outsource partner of the right size, compliance and industry expertise, there are other key factors to consider. How long has the company been in existence? What is its track record of delivering successful projects on time and at cost? How many repeat customers have they had? What is the breadth and size of your potential partner's engineering team? How long have they worked together? Do they have the skills required for your project or will they have to develop them? Do they have a history of being responsive and communicative with their partners? What is their project management style? Is it compatible with your company's? What is their history of regulatory compliance? Getting the answers to these questions up front can help quickly narrow down the potential pool of outsourcing partners, as well as saving a great deal of time, money and frustration.

Finally, you need to consider the kind of working relationship you want to have with your partner. Do you want a very close association with a lot of communication between your team and theirs? Would you rather have a more hands-off approach, where you provide them the project specifications and expect only periodic updates unless a problem arises? Is their preferred working relationship compatible with yours? Getting the answers to all these questions will

require research in terms of formal references, word of mouth from others in your industry and online research, but the time spent researching your potential partners up-front will pay dividends in the long run.

Conclusion

A number of factors are causing American companies to question the economic benefits of offshoring. The dramatic rise in foreign labor costs and the continued superior productivity of American workers have been key drivers in the reconsideration of what had once seemed good economic policy.

Data from surveys conducted over the last two years by BCG of more than 200 American companies currently involved overseas manufacturing show that a growing number of companies are seeing the economic benefits of moving their manufacturing operations back home. According to BCG, in just the last year, there has been a nearly 20 percent increase in the number of companies considering reshoring and a doubling in the number of companies engaged in or actively planning to engage in reshoring in the next couple of years.

The cost and logistical challenges of reshoring are probably two of the biggest factors that hinder more companies from taking advantage of its potential economic advantages. Partnering with a domestic outsourcing company offers reshoring companies a means of minimizing the pain involved in moving their manufacturing back to the U.S. Not all outsourcing companies are equal, and it is critical that a company considering such a partnership ask the right questions and do the necessary research to ensure that the outsourcing partner they choose has the necessary skills and attributes. However, making the right choice in an outsourcing partner can help a company minimize both the cost and challenge of the reshoring transition, while making the move essentially transparent to its customers.

About the Author

Mark Danna has more than 20 years of experience in leading complex capital equipment development, in the areas of mechanical, software, electrical and process integration. Prior to joining Owens Design, he held positions as vice president of engineering development and vice president and general manager of the Substrate Management Group at Asyst Technologies. Before that, he served as vice president of product development for the APCVD product lines at Watkins-Johnson Company. He holds a BA in marketing from the University of Utah, a BS in mechanical engineering from the University of Santa Clara, and pursued graduate studies in advanced dynamics and controls at the University of California, Santa Barbara.

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205 deaths every day, cancer is the
leading cause of premature death.

New biotech concept

The dynamic development of the biotech sector has resulted in an increased number of biotech projects and customers worldwide during the past few years, in particular in the emerging markets. NNE Pharmaplan is seeing many smaller, more flexible biotech facilities based on single-use technology, especially in China.

As a response to these new requirements, NNE Pharmaplan has established a standard biotech facility concept called Bio on demand™, which can be built on site in the traditional way or off site as a modular facility.

Standardised process and utility modules are combined in various ways to accommodate all the different functions in a modern biotech facility and the need for flexibility and adaption to local building and GMP regulations and practices.

The Bio on demand™ concept includes the engineering and supply of a facility as well as related quality systems, standard operating procedures (SOPs) and the organisation of necessary quality tests.

NNE Pharmaplan is currently applying the standard Bio on demand™ concept in the design of a number of new biotech facilities.

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Application of Lean Six Sigma to Optimize a Legacy Cleaning Process

by Emmet Manning, Brian Earls, Keith Bader, Fearghal Downey, PhD, and Kelly Scalva

This article presents a successfully structured, data driven, cross-functional team approach for implementing an improved automated cleaning process, which reduced the overall duration for decontamination and cleaning.

Team Overview

The team for this project included personnel from Merck, Sharp & Dohme (MSD), otherwise known as Merck & Company in North America, a multinational manufacturer of pharmaceuticals and consumer healthcare products to improve people's health and well-being, and Hyde Engineering & Consulting (Hyde), a global design, engineering, and experimental testing organization with specialized expertise in cleaning technologies for process improvement. The case study discussed in this article stems from work completed at the Swords, Dublin, Ireland manufacturing site.

Define

The Problem

A legacy cleaning process for the removal of a product residue containing significant amounts of the Active Pharmaceutical Ingredients (APIs) residue was identified by the engineering team as both a potential safety hazard and a known bottleneck in the manufacturing process - *Figure 1.*

The cleaning process could take up to five working days for Clean in Place (CIP) operations. The long duration of the cleaning process was due to an inconsistent cleaning cycle that did not completely remove the hormonally bases oral solid dose residue from the process equipment. Due to the inconsistent nature of the residue removal, the process routinely required manual intervention, including confined space entry resulting in a breach of the room integrity. As the product residue represents the highest danger at a Level-5 on the Occupational Exposure Band (OEB), manual cleaning was not desirable.

Figure 1. Residue deposits on recirculation pipe for granulate after CIP.

Faced with increased market demand and capacity constraints imposed by the cleaning cycle, and a need to improve operator safety, a project was initiated to increase capacity by dramatically improving cleaning process efficiency.

Project Goals

A safe, robust, reliable, Clean in Place (CIP) process was needed for operational activity and market supply. Key project goals were:

- Reduce the CIP time so that with existing equipment capacity, market demand could be met.

- Significantly improve robustness and reliability.
- Eliminate confined space entry (and thus operator risk).
- Reduce manual cleaning to a minimum.

Detailed Review of the Previous State

A mixer is used to blend basic granulate and dry powder blend with a variety of API's within the OEB5 high containment suite. In January of 2012, a cleaning event for the mixer called attention to the need for process improvement. A review of the process identified the mixer as one of the most difficult pieces of process equipment to clean with frequent requirements for manual cleaning. Initial estimates to upgrade the cleanability and degree of automation were three months; however, a subsequent and more detailed assessment of the project revealed a scale and complexity that would require five months for project completion.

In order to minimize downtime, it became clear that the project would need to be efficiently managed to meet this timeline. Accordingly, the project was governed by Lean Six Sigma (LSS) principles via the Define, Measure, Analyze, Improve, Control (DMAIC) approach, an approach regularly used at the facility for complex projects. Further, individual portions of the process were conducted in accordance with the process validation lifecycle model in which the cleaning process was redeveloped at the bench scale, transferred and tested to a pilot scale tank, translated to the manufacturing equipment, and finally monitored in the third stage of the process validation. The final control phase is continuous, utilizing a Proactive Process Analysis (PPA)/Continuous Process Verification (CPV) approach.

Measure

A thorough risk assessment to review historical data and issues with the cycle processes in terms of both chemical and mechanical failures, deviations, work orders and known issues was undertaken to establish a complete understanding of the process.

This thorough Failure Mode and Effective Analysis (FMEA) approach indicated that there were multiple significant variables that affected the overall success of the cleaning process. These unreliable processes centered on issues with the detergent dosing reliability, system drying robustness, removal of non-soluble excipients; spray ball fouling with insoluble ingredients. Poor spray ball design and fouling of apertures required the replacement and installation of new spray balls. Along with a legacy CIP cycle which did not work effectively requiring greater understanding of optimal parameters and a new cleaning cycle recipe.

In order to successfully implement significant changes in the process cycle, it was important to assign a dedicated cross functional site team with a clear link to the site priorities and deadlines. Proper project planning with key milestones and timelines directly led to the triumph of this project with a balance of time and resource budgeting.

Concurrent Activities – International Cross-Functional Engineering Team

A dedicated cross functional team of cleaning experts was established to focus on the key issues around improvements to the CIP cycle and recipe. This team encompassed international engineering expertise outside the capabilities of the manufacturing facility with a team of consultants that could dedicate the time and resources to complete the project on time and under budget. The consultant company was able to assist with both a local presence on the manufacturing floor on site in Ireland, as well as employ the resources of a specialized cleaning process development and testing laboratory in the United States. Utilizing an international team allowed for a realistic yet compressed project timeline as simultaneous project efforts could best facilitate the change needed in the facility.

Analyze

Actions on the Process Floor and Laboratory Teams

The engineering project manager on the process floor was a key facilitator in determining project challenges and communication link for the potential impacts to the external consultant laboratory personnel. Maximizing the communication paths between the facility and the testing lab, ensured a well-established flow of work and allowed both teams to work in parallel, but to be independently efficient.

Without having to wait for the final completion of the laboratory work, it was possible to communicate daily with the laboratory engineer. The international aspect of these "check-ins" was crucial for the project schedule as the laboratory engineer would complete one pilot scale experimental recipe late in the evening USA time, communicate the data to the Irish team, and team in Ireland would then have a full work day to review the data before discussing the path forward with the Lab at the start of the USA work day. This efficient concurrent problem solving approach maximized the personnel time and resources without bottlenecking the experimental process.

Experimental Small Scale Trials

Laboratory small scale and pilot scale trials were employed to develop a robust/reproducible cleaning cycle. These developmental cleaning studies were conducted on a bench scale level by evaluating the performance of a particular set of parameters, visual, gravimetric, and rinse sampling assessment methods.

To determine optimal cleaning chemistry, temperature, cleaning agent concentration and cycle duration bench scale studies has been demonstrated to be of considerable benefit. For almost any issue, the testing lab has a standard set of

experimental tests to evaluate and filter out the possible cleaning issues. Each approach draws on the a Design of Experiments (DoE) testing model with most residue assessment experiments beginning with an evaluation of the Worst Case Residue(s), although in regard to this specific facility, the two problem residues had already been identified. With the worst case residues in hand, the cleaning chemistry is evaluated to select the most efficient cleaning agent, and is completed by testing process soils with differing acid, alkaline and neutral cleaning agents. Once an appropriate cleaning agent has been determined and approved by the manufacturing facility, a design space exploration study is conducted to assess the cleaning process response to a range of cleaning agent concentrations, temperatures and flow rates (flow rates are evaluated using Reynolds number). With all of the Critical Process Parameters (CPP) defined a cleaning contact time evaluation can determine efficient cleaning cycle durations. These bench scale cleaning studies were completed by using gravimetric means, and made use of small samples (called "coupons") representative of the Material of Construction (MOC) of the process mixer (316L stainless steel).

The design space exploration was conducted using a Design of Experiments (DOE) methodology that allows multiple variables to be modified simultaneously in a prescribed manner such that more information regarding the individual variables may be extracted from experiments than an equal number of experiments in which variables are individually modified.

For the design space exploration, a composite design in which turbulence, concentration and temperature were varied to produce a response surface that characterizes the removal rate over the defined design space, shown pictorially in Figure 2. This portion of the study consisted of 20 treatment conditions with four replicates for each treatment condition generating a total of 80 data points.

In order to properly simulate conditions for large cleaning processes at the bench scale, large scale conditions using parameters that translate well or that are insensitive to process scale needed to be addressed. The four basic critical cleaning process parameters of importance to cleaning must be maintained. Those conditions are 1. the mechanical energy imparted to soils during cleaning, 2. temperature of cleaning solutions, 3. cleaning agent concentration, and 4. the duration that post production residues and equipment surfaces are exposed to cleaning solutions. Of the four parameters, the last three scale directly between developmental and manufacturing scale equipment. However, the first of these parameters, mechanical energy, is dependent on scale of the equipment and must somehow compensate for size differences. For this study, Reynolds number, a dimensionless parameter quantifying turbulence was used as a means of characterizing mechanical energy. A Reynolds number of 4,000 simulates the mass transfer effect of a turbulent falling film in a vessel and was used for all cleaning agent selection treatment conditions.

The initial duration for the cleaning tests was determined through initial range finding tests. Further, with all of the degrees of freedom for the system constrained (temperature, concentration, external energy, and duration); the bulk removal rate of the production residues then becomes a determinant for identifying the worst case residue.

The agitated immersion testing system, Figure 3, allows for the control of each of the critical cleaning process parameters. Temperature is maintained through a Proportional-Integral-Derivative (PID) controlled water bath. Cleaning solutions were prepared at the desired concentrations in a 1000 mL beaker and placed within the water bath. The agitation rate was set by a stir plate and confirmed with the use of a digital laser tachometer. Coupons where then submerged into the 1000 ml beaker filled with a specified cleaning agent, concentration, temperature and agitation rate.

To quickly conduct multiple iterations and replicates, an agitated immersion scheme was used, where each run allowed for the simultaneous testing of two coupons. In order to have enough data to calculate a standard deviation, four coupons were run for each treatment condition; the duration of each run was determined through range finding experiments and did not vary between treatment conditions of the same detergent. A second set of coupons was then run using the same conditions. The coupons were submerged in the

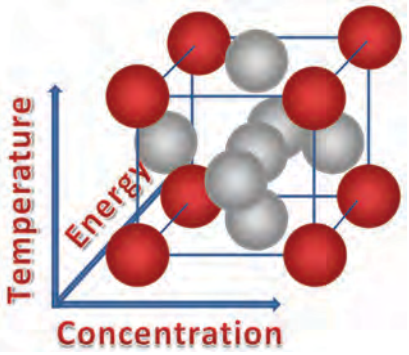

Figure 2. DOE composite experimental design with center points.

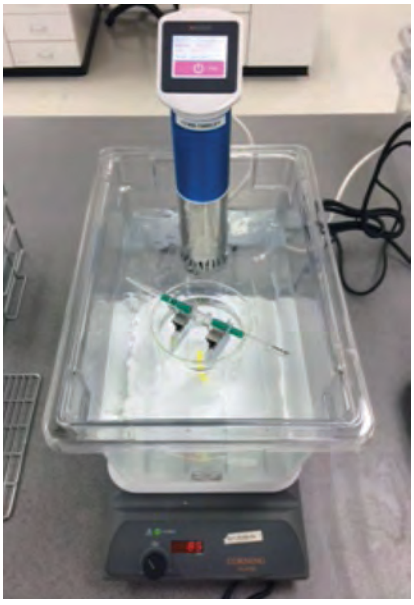
Figure 3. Agitated immersion scheme.

solution after removal from the solution the coupons were dried in a low temperature gravity convection oven. The test was designed to leave approximately half of the spiked residue on the coupons, which was determined gravimetrically with measurements taken both before and after subjecting the coupon to the testing solutions.

Interestingly some of the preconceived perceptions around what the 'best' cleaning parameters were proved to be incorrect through the data collected in the laboratory testing. It is commonly assumed that with the increase in cleaning agent concentration and cleaning temperature, the process will be improved; however, testing indicated that the highest removal rate would be dependent on use of high cleaning temperatures (65°C) and low COSA-CIP-92 detergent concentrations (0.5% v/v). For these specific residues, conclusions for the bench scale testing indicated that residue removal was dependent on both the temperature and concentration of the cleaning agent, as changes in the Reynolds number did not appear to have any significant effect on rate of removal, any turbulent regime would be sufficient for the cleaning cycle.

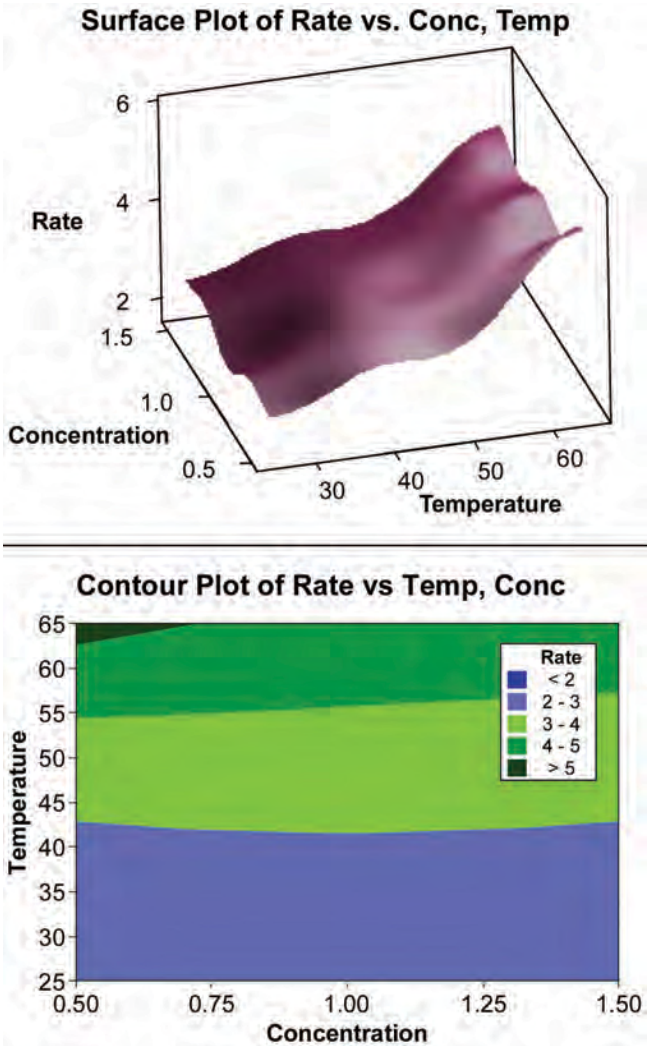

Figure 4. Surface and contour plots of removal rate vs. concentration and temperature.

As the pharmaceutical manufacturer was interested in reducing environmental health and safety as well as economic impacts of the detergent use, the lower detergent concentration was favorable. Although it was found that the acidic cleaner, COSA-CIP-72, had slightly improved residue removal rates, given the timeline of the project and the expenses associated with making a change to the currently employed cleaning agent, the slight increase in removal rates were not significant enough to justify employing an acidic cleaning agent. The testing also indicated that replacing the foremost cold water rinse with a hot water rinse would increase residue removal rate by more than 1.5 times that of the current cold water rinse.

Figure 4 shows both a contour plot and a response surface plot for the cleaning process response to changes in the critical cleaning process parameters. Notably, lower cleaning agent concentrations were shown to have a positive impact on rate. This can be seen in the top left corner of the contour plot in which the color-coded scale reveals that that the highest rate of removal corresponds to a combination of the lowest concentration and highest temperature. Specifically, for a cleaning agent concentration of 0.5% and a temperature of 65°C, the rate of residue removal is highest, thereby producing a shorter cleaning duration. The response surface plot is a three dimensional representation of the cleaning process response to critical cleaning process parameters, and also reflects the importance of using a higher temperature to greatly decrease the duration of the cleaning cycle.

While the box plot in Figure 5 provides a representation of the same information shown in the contour and surface plots shown in Figure 4, it provides a means to visually assess the data and determine if the results are statistically significant through graphical representation of variability. Further, both the response surface and contour plots are

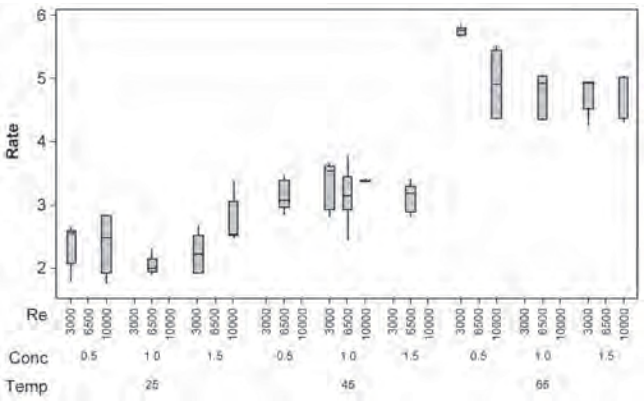

Figure 5. Box plot of removal rate vs. concentration and temperature.

intrinsically limited to plotting the response to two of the critical process parameters (temperature and concentration) whereas the box plot allows for interpretation of the data with respect to all three factors (temperature, concentration and turbulence) chosen for the designed experiment. The factors are compared by the rate of removal, and are shown first with "Re," or the turbulence or Reynolds Number (unit less), "Conc" used for the concentration of the COSA-CIP-92 detergent (in units of [% v/v]) and "Temp" (Temperature in °C). In this case, the design space reveals that the cleaning process response is relatively insensitive to the impact of turbulence or concentration and more highly influenced by temperature.

Pilot Scale Trials

The pilot scale cleaning study was completed to confirm the determined effectiveness of the potential cycle development recipes derived from data taken from the previous bench scale testing and to provide increased confidence and reduce risk when transferring to full scale. Pilot scale testing was conducted in the cleaning process development test lab in the United States. Testing was conducted first with a control cleaning cycle with cycle parameters that were representative of the existing cycle parameters used at the Ireland Manufacturing site. Specifically, the control run testing served as a baseline against which developed cycles could be compared. To ensure that the cycle parameters for the control cycle were representative, rinse and wash volumes were scaled down from the maximum CIP make up volume employed at the manufacturing site using a ratio of surface area between the manufacturing and the pilot scale equipment (1200L v 40L). To gain a better understanding of the pilot scale design space, successive runs were conducted in which the rinse volumes were reduced by a percentage factor until the parameter set leading to the edge of failure was identified. Assessments for this exercise were based on a visual assessment of the pilot scale test vessel.

The pilot scale test system employed to investigate the efficacy of parameters determined during bench scale cleaning studies is shown in Figure 6. The system allowed for the control of each of the critical cleaning process parameters of temperature, concentration, and flow rate. Temperature was maintained through the use of a 110 VAC resistive heating element in the supply tank. The supply tank has a maximum working volume of 117 L and was used to batch cleaning solutions at the preferred concentration and temperature for pilot scale testing to replicate the system utilized on site.

Conductivity and temperature were measured through probes placed in the supply tank. The 39 L pilot tank was fitted with a center mounted fixed spray device with a 180° up spray pattern designed to create a turbulent falling film on the sidewall of the vessel. The vessel permitted the application of post-production residues to the vessel internals as well as visual inspection through a widened access space comprising slightly less than half of the top dome.

A recirculation line from the tank to the supply tank is shown in Figure 6 and was only used during the control runs and not for any of the experimental test recipes as the site had previous issues with the recirculation of the detergent wash fouling the spray balls with insoluble talc from the product formulation. There was a slight delay between hot solution steps in the cleaning process, as solutions in the supply tank required time to reach temperature. This is in line with the dwell time experienced during commercial CIP of the mixing vessel.

The external energy for the cleaning process, in the form of turbulence, was characterized in terms of the Reynolds number, as it is replicable over various geometry conformations it was utilized to translate from the small scale to the pilot scale and finally to the manufacturing floor.

Riboflavin Spray Coverage Testing

Spray pattern coverage testing was conducted before the vessel was spiked with placebo residue to ensure that all surfaces to be spiked could be adequately contacted by directly impinging sprays or through a turbulent falling film.

Testing was accomplished through the use of riboflavin (0.2 g USP Riboflavin/liter of solution), a fluorescent indicator sprayed on the equipment surfaces with a hand held spray bottle that was capable of producing a fine mist, and allowed to dry completely before conducting a rinse.

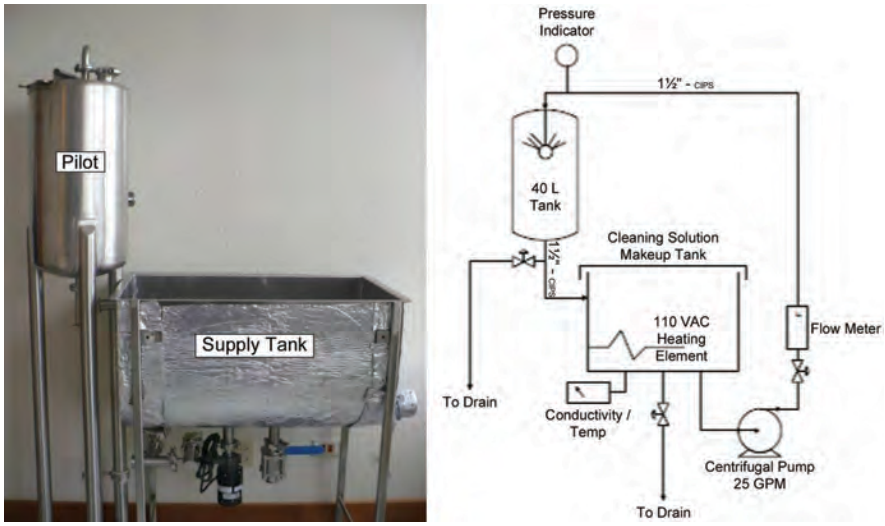

Figure 6. Pilot scale experimental set up.

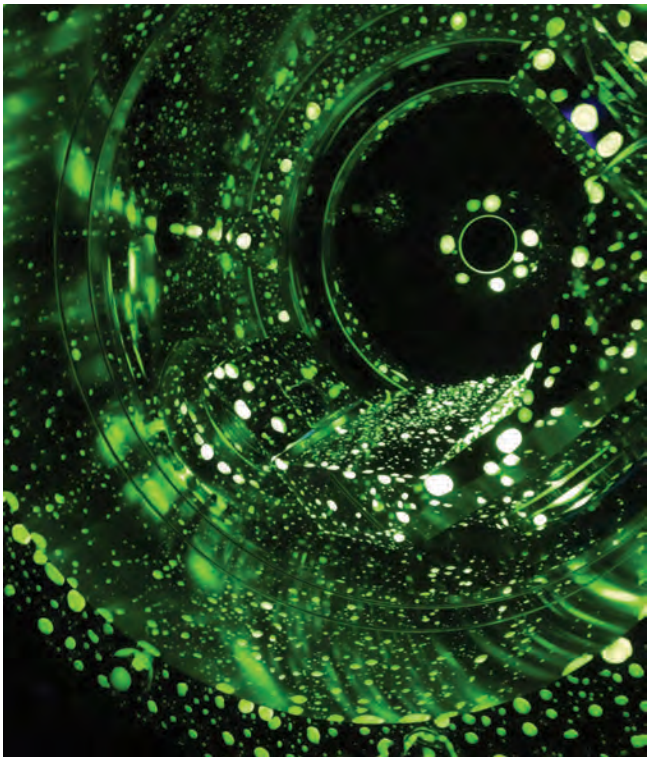

Figure 7. Typical image of riboflavin vessel testing.

As riboflavin coated surfaces will fluoresce only when wet, complete riboflavin application was verified when wet using an ultraviolet light source (285 nm emission wavelength) to observe any residual riboflavin through its characteristic green fluorescence, Figure 7. Since riboflavin is only slightly soluble in water, dissolution of material deposited on the surface after drying is much harder to remove than solutions that are not allowed to dry. Brief burst rinses are typically employed in CIP cycles to flush residues from the system; however, because of this limited solubility, removal of dried riboflavin in locations not receiving directly impinging rinse water may be limited. Accordingly, locations that exhibit riboflavin after rinse testing do not necessarily indicate a spray coverage failure. Rather, these locations may represent more difficult to clean "worst-case" sites that may receive less mechanical energy imparted by directly impinging spray. As absolutely no fluorescence was observed after a rinse cycle with distilled water, the riboflavin spray pattern coverage test for the pilot scale test system was considered successful with all surfaces adequately contacted with fluid.

Improve

Residue Simulation

A placebo residue was formulated without the Active Pharmaceutical Ingredients (APIs) to simulate a post-production residue representative of that at the facility, but easier and safer to handle. Residue is shown in both Figure 8 and Figure 9.

The placebo suspension was applied to the sides of the pilot tank using a hand held spray bottle capable of producing a fine mist. To attain complete tank coverage, the residue was sprayed onto the surface of the tank, starting from the bottom of the tank and ending with application to the top dome. In order to simulate a worst case post production soil load, every attempt was made to uniformly coat the surface of the tank with the residue in the same fashion for every experimental run. After applying the placebo to the surface of the pilot tank, the residue was allowed to dry completely at ambient conditions for at least 6 hours, before testing.

Throughout the pilot scale testing, the worst case cleaning conditions were utilized. The pilot scaled test tank was soiled using a greater quantity and concentration of placebo residue than encountered in the actual process equipment. The lowest possible flow rate to create a turbulent falling film was used for testing. Further, only one fixed spray device was employed in the pilot tank, whereas the process

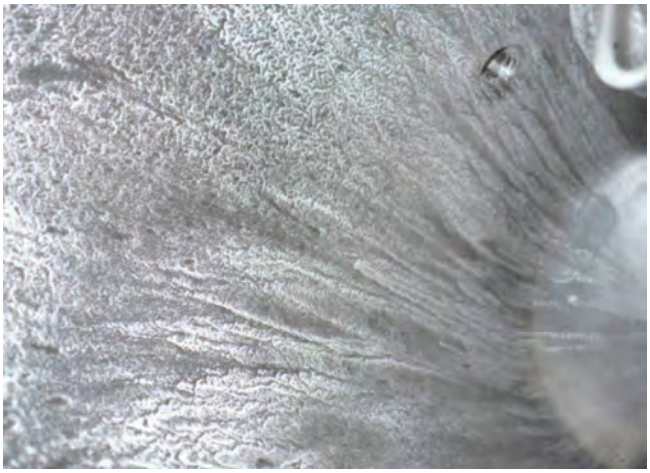

Figure 8. Dried residue sprayed in the interior of the pilot tank.

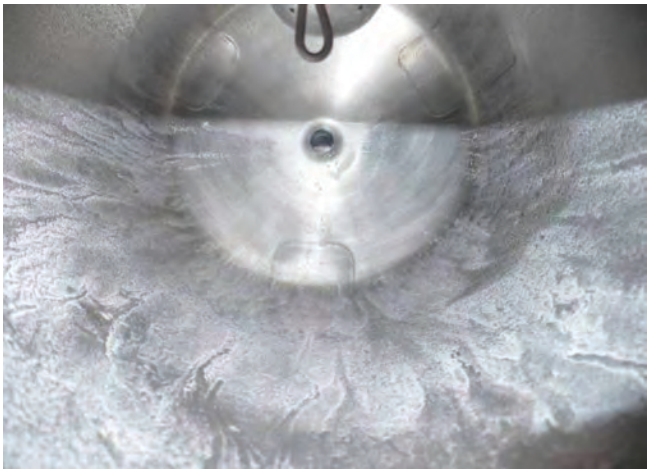

Figure 9. Dried residue sprayed in the interior of the tank.

Figure 10. Clean tank after testing.

mixer employed on site had nine spray devices, all of which are rotating sprays that rely on higher energy directly impinging streams of cleaning solutions.

The testing produced a robust cleaning cycle with four cycle phases, operating at 65°C, three of the phases consisting of process water rinses, and one chemical wash phase consisting of a 0.5% concentration of COSA-CIP-92, capable of completely removing the placebo residue. The proposed cleaning cycle was tested to the edge of failure by reducing rinse volumes in all four phases by 10%, using the worst cleaning conditions to ensure the strength of the cleaning formulation. This cycle passed thus proving the effective robustness of the proposed cleaning cycle, as shown in Figure 10.

Control

Robustness Pilot Scale Testing

The edge of failure was successfully tested once the cleaning cycle control run passed. After a cleaning cycle was successful, it was reduced by volume by 25% where it failed, so then the cycle was reduced by a 15% volume and it also failed; however, it passed with the 10% reduction in volume, proving its robustness.

Successful Implementation from the Laboratory

A decision was made to carry out a near 'in parallel' approach of laboratory testing closely followed by on site modifications to accommodate the lab findings. The recipe robustness determined off site at the lab was coupled in parallel to some significant CIP improvements implemented on site. Parameters of contact time and temperature were evaluated (all other parameters fixed). A decision on detergent selection was fixed with COSA-CIP-92. Reynolds number mimicking turbulent flow was maintained during pilot studies, again to mimic the anticipated conditions found in the mixer. Effectiveness of straight through rinsing versus recirculation was evaluated. Process optimization on pilot scale allowed for more rapid implementation with greater sense of confidence for Right First Time (RFT). In the pilot scale, the recipe was successfully tested to "edge of failure," which would not have been possible at the site due to time and cost constraints. The pilot study was performed on a 'worst case' basis (single spray ball at lower pressure versus multiple spray balls at higher pressures), thus increasing confidence.

Not all the Laboratory (experimentation) recommendations were possible due to facility limitations – i.e., make up volume of CIP solution, although the remote team was able to optimize the solution based on the available equipment, and additional constraints.

Concurrent Activity on the Process Floor

As a result of the FMEA carried out by the site based team and augmented by the laboratory/pilot scale activities, the following changes were approved and scheduled within the project timelines:

Mechanical

- Replaced existing spray balls with new spray ball design (greater cleaning efficiency)
- New pipe work and spray ball locations in mixing vessel based on computer imaging (complete spray coverage)

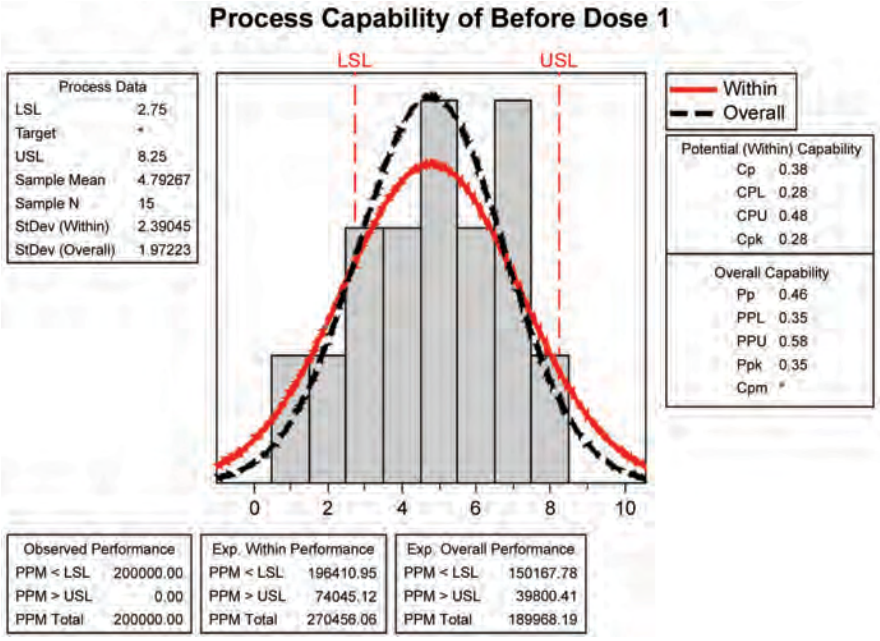

Figure 11. Process capability before improvements.

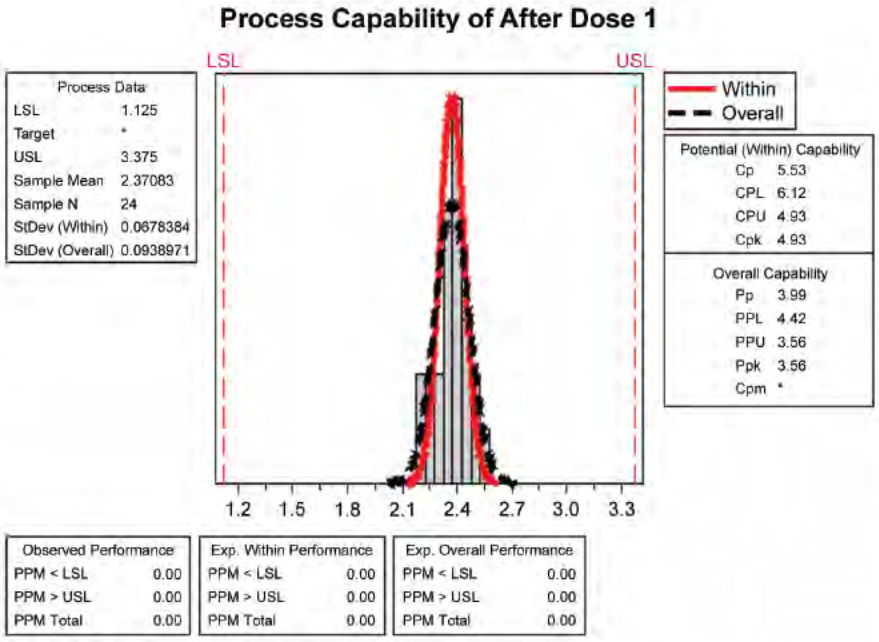

Figure 12. Process capability after improvements.

- New 6kW air heater (increased thermal mass)
- New air supply header (continuity of air supply)
- New conductivity probe (guarantee homogeneity of CIP solution)
- New detergent pumps and set-up (obviates air locks and priming issues)

Automation

- A new recipe designed from first principles to clean and dry
- New intelligent detergent dosing program incorporated

Scale-Up of Development and Pilot CIP Process

- New designed recipe, developed at the lab introduced to production scale
- Successful riboflavin and "edge of failure" performed
- IQ/OQ/PQ/CV successfully complete on schedule/budget

Outcomes

After successful installation, commissioning and qualification of the aforementioned modifications, the system was tested in earnest and the following outcomes were achieved:

- 100% CIP cycle success rate (n = >24)
- Reduction in CIP cycle turnaround time from 5 days to 23 hours
- Eradication of confined space entry requirement
- Eradication of manual cleaning for the mixer ports
- 25% reduction in actual CIP cycle time
- 35% reduction in detergent usage
- Eradication of detergent pump air locking and leaking
- 33% reduction in purified water usage
- Equipment and CIP routes 100% dry
- Common CIP cycle for 2 separate products
- Detergent dose failures eradicated

Not only did the project deliver an increase in process capability (Cpk) from 0.28 to 4.98 as shown in Figure 11 and Figure 12, but it also realized an 80% improvement in turnaround time. Further, there were a significant number of additional benefits including an improvement in operator safety, a reduction in operating expenses, and eradication of previous equipment failures, all delivered within the budget and timeline. Finally, the entire project team was also able to take pride in a successful "real-life" implementation of Lean Six Sigma principles by an integrated, highly motivated intra-organizational team.

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A Review of the Regulations and International Developments on Quality and Supply Chain Integrity of Pharmaceutical Excipients

by Sia Chong Hock, Sean Lee Ji Yang, Vimal Sachdeva, and Chan Lai Wah

This article presents an overview of the regulations and international developments on quality and supply chain integrity of pharmaceutical excipients, analyzing the challenges faced by regulatory authorities with recommendations to improve the excipient control framework.

Pharmaceutical excipients are substances other than the Active Pharmaceutical Ingredients (APIs) which are included during the manufacturing process or are contained in the Finished Product (FP) as part and parcel of its formulation.[1] Pharmaceutical excipients include diluents, disintegrants, lubricants, solvents and co-solvents, anti-oxidants, flavoring agents and anti-microbial preservatives. While APIs have the key function of producing therapeutic effects in the body, excipients in the FP serve other functions, such as enhancing stability, bioavailability or patient acceptability of the FP.[2]

Historically, excipients in pharmaceutical formulations were viewed as inert ingredients contributing generally to the stability of the FP. As the pharmaceutical industry became more focused on faster time to market, new manufacturing processes, such as direct compression, fluidized-bed granulation, automatic capsule filling, and film coating were introduced.[3] Even the production equipment, such as ampoule-fillers, tableting and encapsulating machines, had to be re-designed to work at high speeds. New and improved excipients were required for compatibility with both modern processes and production equipment. Moreover, the interest in new therapeutic systems and modified-release dosage forms also has led to the demand for more sophisticated excipients that can fulfil specific functions within the formulations. These innovative formulations can optimize the pharmacokinetics of the

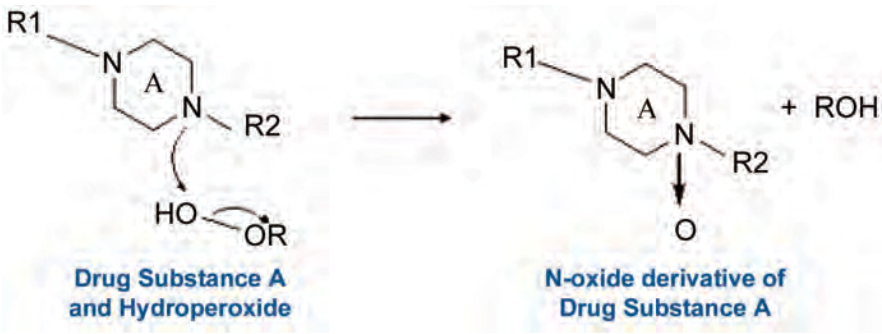

Figure 1. Reaction of piperazine in Drug Substance A with hydroperoxide impurities of crospovidone.[14]

FP, increasing efficacy and improving patient's compliance, thereby giving value-add.[4] In view of the new and emerging roles of excipients in pharmaceutical formulations, they are no longer considered "inactive or inert ingredients."[3,5]

Water is an excipient that is widely used as a solvent or vehicle in the manufacture of FPs. However, unlike other excipients, water is not procured from commercial suppliers, but produced in-house by FP manufacturers[6] in compliance with pharmacopoeial monographs and Good Manufacturing Practice (GMP) standards for FPs, such as those of the Pharmaceutical Inspection Convention/Co-operation Scheme (PIC/S)[7] and the World Health Organization (WHO).[9] As water for pharmaceutical use is produced "in-situ," there is virtually no supply chain integrity issue; therefore, water as an excipient will not be elaborated in this review.

In terms of overall composition of a FP, the percentage of the API in the formulation is considerably lower vis-a-vis that of the excipients. Therefore, any quality defect arising from excipients, e.g., microbial contamination or unacceptable levels of reactive impurities, may be more detrimental than a defective API in the formulation.

The microbiological quality of pharmaceutical excipients may significantly affect the processing and physical stability of FPs, which may lead to patient safety issues in patients.[10] Furthermore, some excipients are produced for use in the food or agricultural industries and not specifically for the pharmaceutical industry.[4,5] Hence, the microbiological quality control of such excipients may be less stringent. However, examinations of pharmaceutical excipient samples revealed only a minority which exceeded pharmacopoeial limits for microorganisms.[11,12] These findings may be attributed to the observance of good practices by the suppliers to control the microbial limits of excipients. Hence, this review will only focus on quality issues arising from chemically reactive impurities in pharmaceutical excipients.

Current Issues and Challenges

Chemically Reactive Impurities in Pharmaceutical Excipients

Reactive impurities in pharmaceutical excipients could cause drug product instability, leading to decreased product performance and/or formation of potentially toxic degradants.[13,14] Hydroperoxides are common peroxide impurities in pharmaceutical excipients and play a major role in drug degradation.[15] In 2009, the United States Food and Drug Administration (US FDA) detected excessive levels of peroxide in a batch of crospovidone manufactured in China.[16] Other batches of povidone analogues, from the same manufacturer, were also discovered to contain excessive levels of peroxide.[17] High temperatures used in heat-drying processes generate higher levels of hydroperoxide impurities than freeze-drying in povidone analogs.[18,19] Any API that is prone to oxidation is potentially susceptible to interactions

with these hydroperoxide impurities, which may lead to the formation of N-oxide (Figure 1),[20,21] oxidation of thiols,[22] and/or abstraction of benzylic hydrogen atoms,[23] and resultant degradation of the API.

Trace levels of reducing sugar impurities can be found in excipients, such as microcrystalline cellulose[24] and mannitol.[25] These impurities could be generated as by-products from manufacturing processes, such as acid hydrolysis and milling or as degradation products of polysaccharide excipients during long-term exposure to unfavorable storage conditions, such as heat and moisture. These impurities can interact with amine groups of APIs via the Maillard reaction (Figure 2),[26] resulting in loss of therapeutic activity.

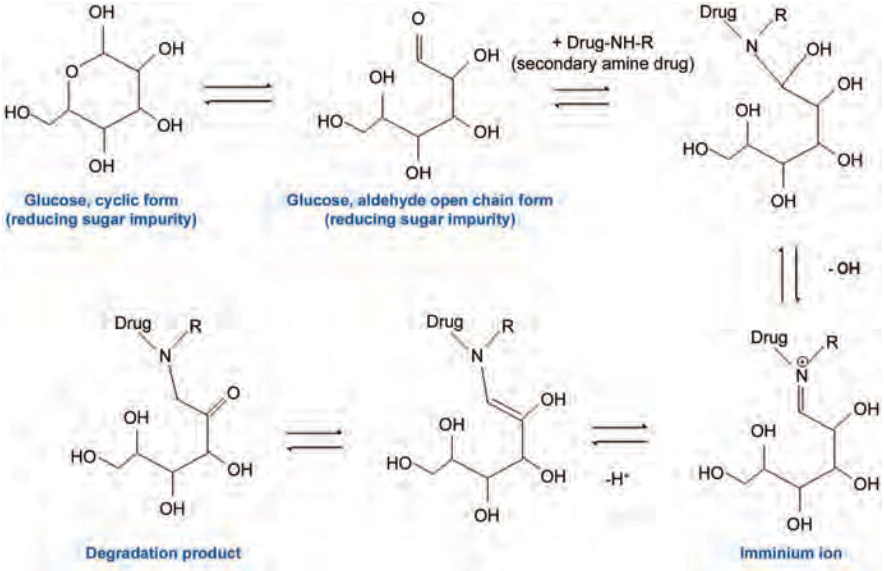

Figure 2. Maillard reaction of secondary amine drug with reducing sugar impurity, resulting in the formation of Amadori rearrangement product.[13]

The levels of reactive impurities in excipients may vary between lots and vendors. It is therefore pertinent to regulate the level of reactive impurities through compliance with GMP and Good Distribution Practices (GDPs).

Industry Globalization and Excipient Adulteration

The pharmaceutical industry is highly globalized, resulting in an increasingly complex supply chain of FPs and excipients, which may create opportunities for counterfeit or substandard excipients entering the supply chain.[3,27] In 2006, 115 individuals in Panama died after receiving cough syrup containing glycerin – an excipient that was adulterated with toxic diethylene glycol (DEG) - *Figure 3*. The contaminated glycerin was traced back to a chemical manufacturer in China which was not approved to manufacture pharmaceutical ingredients, and which falsely attested to the purity of the glycerin in the certificate of analysis. The adulterated glycerin passed through several brokers located across three continents (Figure 4), who resold it without specifying the previous owners or performing any purity tests (Figure 5).[28] Similar cases of adulterated glycerin also have happened in Haiti (1995 to 1996),[28,29] Nigeria (1990 and 2008),[30,31] and India (1986)[32] due largely to the lack of regulations and controls on the quality of pharmaceutical excipients and their supply chain.

Current Regulatory Controls of Excipients

Regulations for excipients may vary among Regulatory Authorities (RAs). Details of regulatory controls by various RAs are described in Table A. Unlike APIs and FPs, excipients receive very little oversight from RAs.[35] Currently, inspections are focused on FP and API manufacturers, with little attention paid to excipient manufacturers, who may be inspected only when an excipient poses risk to patients or if a new excipient is introduced.[36]

As seen in Table A, legislations and regulations which will change how excipients are sourced and controlled in the future are being developed and implemented.[37,38] The Food and Drug Administration Safety and Innovation Act (FDASIA), established in 2012, will help the US FDA deal with the increasing complexity of globalized supply chains. This will in turn help to ensure the safety, effectiveness and quality of pharmaceutical products and excipients in the US.[39] The European Falsified Medicines Directive (FMD),[40] established in 2011, amends the European Directive 2001/83/EC

Figure 3. The medicines containing DEG-laced glycerin in the Panama incident.[29]

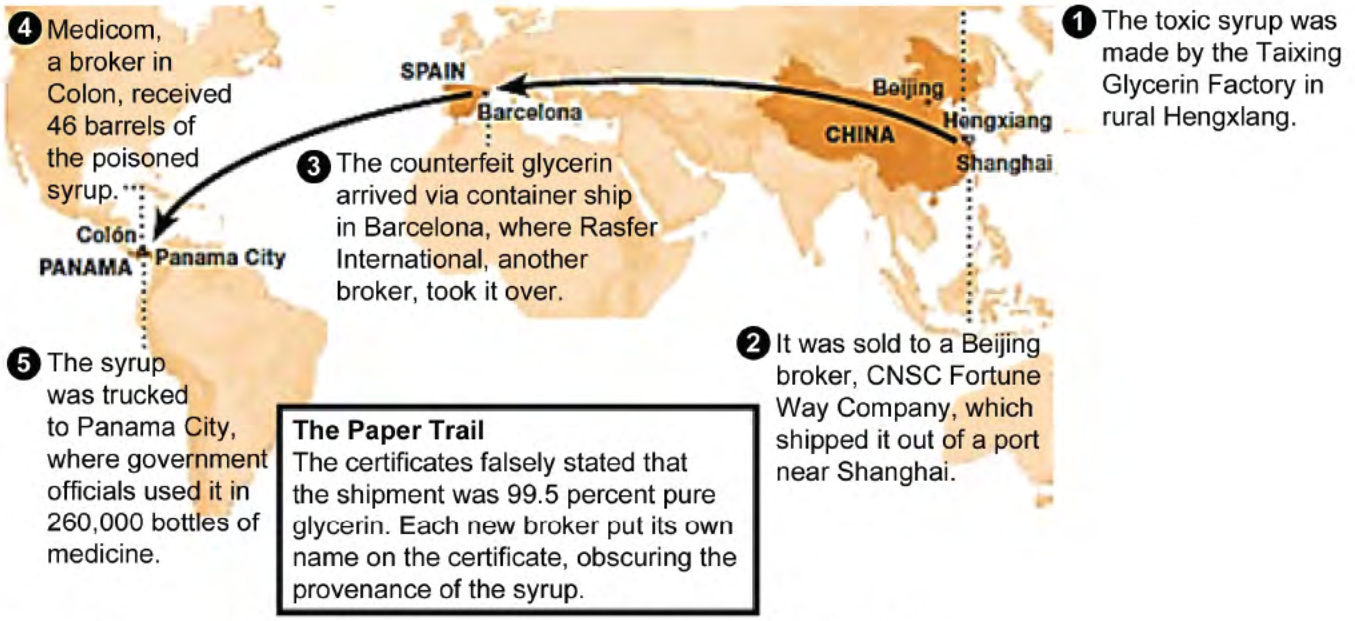

Figure 4. A schematic of the supply chain of the adulterated glycerin in the Panama incident.[33]

"Community Code Relating to Medicinal Products" to help prevent the entry of falsified medicinal products into the legal supply chain of medicines in the European Union (EU).[41] The China Food and Drug Administration (CFDA) imple-

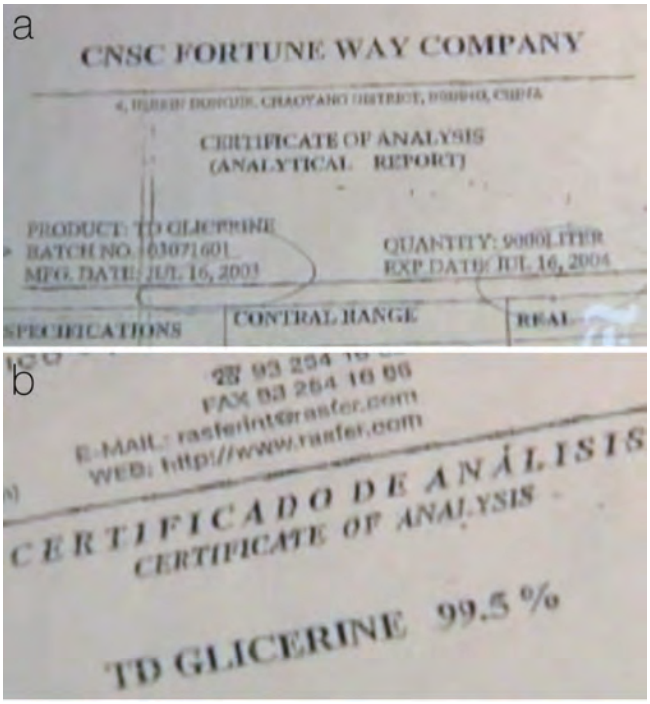

Figure 5. Scans of certificates of analysis from (a) CNSC Fortune Way Company and (b) Rasfer International, "attesting" to the purity of the glycerin without actual QC testing. The name "TD glycerin" was in all the shipping documents. Nobody knew what it meant. It was later revealed that TD stood for the Chinese word "tidai," which means substitute.[29,34]

mented the "Regulation of Strengthening Supervision on Pharmaceutical Excipients" in 2012 to improve the oversight on manufacturing and use of pharmaceutical excipients.[42]

In India, there are generally no specific regulatory requirements for excipients with very limited excipients listed in the Indian Pharmacopoeia - *Table A*.[43,44] Pharmaceutical companies in India implement good practices as a way of voluntary self-regulation.[45] The reason given for the lack of regulatory oversight on pharmaceutical excipients is that India is a relatively new player in the pharmaceutical excipient industry. The Indian pharmaceutical excipient industry is composed of mainly foreign companies which have invested in production facilities in India to exploit its low-cost manufacturing capabilities.[44] With domestic companies anticipated to penetrate the Indian excipient market aggressively, there is a growing need for an organized regulatory framework to be established by the Indian government.[44]

Current Good Manufacturing Practices for Excipients

Under existing GMP, such as the PIC/S Guide to GMP for Medicinal Products, the onus is on FP manufacturers to use quality excipients - *Table A*.[7] Excipient users are usually unaware of the manufacturing process, and are unable to estimate the quality deviation for any given excipient.[64] Sole dependence on compliance with pharmacopoeial specifications or Certificates of Analysis to ascertain the quality of excipients provides no insight into the quality system or GMP compliance of the excipient manufacturer.[64,65] Implementation of GMP provides better quality assurance and control of excipients through adoption of standard processes and practices.[66] Hence, it is highly recommended that pharmaceutical excipient users ensure that their excipients are manufactured in compliance with GMP.[27]

The current Joint IPEC – PQG GMP Guide for Pharmaceutical Excipients[2] was published as a collaborative effort between the International Pharmaceutical Excipients Council (IPEC) and the Pharmaceutical Quality Group (PQG). The WHO is currently reviewing this guide to update its own GMP requirements for pharmaceutical excipients.[67,68] The current WHO GMP for excipients[69] is based on the first edition of the IPEC GMP standards for bulk pharmaceutical excipients.[68] The United States Pharmacopoeia (USP) General Chapter <1078> "GMP for Bulk Pharmaceutical Excipients"[70] also adopts principles from the IPEC-PQG Guide.[71,73] This guide combines the 2001 edition of the IPEC Guide[74] with the PQG's PS9100:2002 Pharmaceutical Excipients Guide. It provides assurance to excipient manufacturers and their customers that excipients manufactured in accordance to this Joint Guide would fulfil ISO 9001 quality management system standard as well as internationally accepted GMPs. This guide, however, has its flaws; it attempts to define requirements in areas such as personnel hygiene, infrastructure, and work environment, which inevitably leads to clauses that may be appropriate only for specific excipients.[75,76]

In response to the above, the NSF 363 Joint Committee, comprising IPEC-Americas and NSF International, an accredited subsidiary of the American National Standard Institute (ANSI), is improving upon the IPEC GMP principles to develop the NSF363 GMP.[77] The latter will be a new American national standard for excipient GMPs. The proposed standard requires application of risk-assessment principles to define and justify appropriate GMP controls in order to mitigate risk in the manufacturing process. This standard will be auditable and applicable across all excipient manufacturing processes, regardless of their chemical and physical properties, and uses in different types of drug products.

Differing Levels of GMP Compliance in Various Jurisdictions

For most RAs, there is no official adoption of GMP requirements for the manufacture of excipients or inspection of excipient manufacturers.

The Japanese Pharmaceutical and Medical Devices Agency (PMDA) does not impose any GMP requirements

on excipient manufacturers.[78] The Japan Pharmaceutical Excipients Council (JPEC) or IPEC-Japan has published a "Self-Imposed Standard of GMP for Pharmaceutical Excipients"[79] as a voluntary GMP for the perusal of excipient manufacturers. This JPEC GMP is a different standard from the PQG-IPEC Guide. Manufacturers may be audited based on this standard by the Japanese GMP Auditing Board for Pharmaceutical Excipients.[78]

The FDASIA clarifies that cGMP for FPs includes the role and responsibility of FP manufacturers to establish the safety of raw materials. This may be inferred as a requirement for FP manufacturers to use only quality excipients manufactured in compliance with GMP.[80] The US FDA does not explicitly promulgate any GMP standard for excipients, but considers any established well-accepted voluntary excipient standards, such as the IPEC-PQG GMP Guide or the upcoming NSF 363 as potentially applicable standards under the National Technology Transfer and Advancement Act (NTTA).[36,81]

Regulators in the EU, including the MHRA of the UK, expect FP manufacturers to define the appropriate level of the EU GMP, via risk-based assessment of the type of excipient. This is to be applied by excipient suppliers to ensure that they comply with the appropriate level of GMP - *Table A*.[82] The risk assessment guidelines are still in the draft stage.[51]

Both the EMA and US FDA conduct inspections on excipient manufacturers using a risk-based approach to assess compliance to GMP.[80,82] The EMA requires the excipient manufacturer to pass an inspection before a GMP certificate is issued,[40] while the inspection by US FDA does not result in any certification. Moreover, the risk assessment guideline of EMA is almost established while the US FDA does not specify any equivalent guideline for the inspection of excipient manufacturers.[80]

CFDA is currently the only RA which has made GMP compulsory for excipient manufacturers - *Table A*.[42] The CFDA GMP for Pharmaceutical Excipients (2006) was mandated as part of the implementation of the Strengthening Regulations in 2012.[83] In addition to mandatory audits to be performed by FP manufacturers on their excipient manufacturers, the

RAs	Details of Regulatory Controls for Excipients
Australia Therapeutic Goods Administration (TGA)	FP manufacturers shall: • Purchase excipients only from approved suppliers. • Discuss manufacturing and quality specifications for the excipients with the suppliers. • Sample and test excipients before use. • Check containers of excipients for integrity of package and seal. • Check that the delivery invoice and labels of the excipient match.[8]
China Food and Drug Administration (CFDA) *Formerly known as State Food and Drug Administration (SFDA)*	FP manufacturers must: • Have an effective quality control (QC) department which ensures that the excipient suppliers are audited before approval of purchase. The QC department shall conduct quality tests on purchased excipients to check for compliance with Chinese Pharmacopoeial (CP) standards.[46] • Set up quality agreements with their excipient suppliers. • Submit excipient information (e.g. excipient name, supplier name, specifications and supplier audit results) in their product registration to CFDA. • Inform CFDA of any change in excipient in their products or change of supplier and submit the relevant documents pertaining to the change, as well as supplier audit results, to CFDA for review before they can be allowed to use the excipient.[47] • Be held responsible if their products contain adulterated excipients. Excipient manufacturers must: • Comply with SFDA Good Manufacturing Practice for Pharmaceutical Excipients (2006).[48] • Accept audits by FP manufacturers and inform the latter of any changes to manufacturing process or raw material source. • Apply for a license to manufacture excipients specified in the CFDA's list of 28 high risk excipients.[49] Provincial FDA will conduct onsite inspection and random tests according to the Excipients Good Manufacturing Practices before granting the license. Others: • Non-routine inspections shall be conducted on excipient manufacturers. • Inspections will be more frequent and stricter on errant manufacturers. Future development: • Excipient manufacturers will be required to submit master files of low-risk excipients to provincial FDA for record. • Excipient registry (or database) shall be established, where FP manufacturers update information on the excipients used in their products and RAs shall update registry information on the production and use of excipients. • Excipient manufacturer credibility system shall be established and made public so that FP manufacturers may review and select excipient suppliers. • The Chinese Pharmacopoeia 2015 edition shall include more excipient monographs while existing excipient monographs shall be reviewed and updated.[50]
European Medicines Agency (EMA)	Falsified Medicines Directive:[41] • FP manufacturers shall ensure that the excipients are suitable for pharmaceutical use by ascertaining the appropriate level of EU GMP to be complied with. This is done on the basis of a formalized risk assessment that takes into account the source and intended use of the excipients and previous incidents of quality defects. • The guideline on this formalized risk assessment has been drafted.[51] • FP manufacturers shall verify that the appropriate standards of EU GMP are applied and documented. • Non-routine inspections of excipient manufacturers or importers shall be conducted unannounced by RAs if: - noncompliance with GMP/GDP is suspected or - requested by the European Directorate for the Quality of Medicines (EDQM) or - requested by the FP manufacturer. Certificate of GMP/GDP/PhEur shall be issued if manufacturers or importers are shown to have complied. EU GMP: • FP manufacturers shall only use excipients from selected suppliers, monitor their suppliers, and verify that each excipient delivery is from the approved supply chain.[52-53] • FP manufacturer and excipient suppliers shall discuss all aspects of the production and control of the excipients, including handling, labelling and packaging requirements.[53] • FP manufacturers shall prepare a Site Master File providing details about the entire supply chain and procedures for suspected adulterated excipients.[54-55]

Table A. Details of regulatory controls for excipients by various RAs.

Strengthening Regulations stipulate non-routine regulatory inspections, indicating the resolve of CFDA to ensure that excipient manufacturers comply with GMP. The CFDA also requires the manufacturers of certain high-risk excipients, a list of which was published in 2013, to be licensed.[49] Considering China's history of adulterated excipients,[28-29] these measures have to be implemented by the CFDA to ensure that the manufacturers produce acceptable excipients.

Consequences of Differences in GMP Compliance

Having different GMP regulatory requirements for pharmaceutical excipients may result in ambiguity regarding compliance and may cause variation in excipient manufacturing and quality.[35,37] For example, there are provisions in the mandatory CFDA GMP for Pharmaceutical Excipients that are not covered by the IPEC-PQG GMP and vice versa, as summarized in Table B.

Although the CFDA GMP for Pharmaceutical Excipients is stringent in its technicalities and specifications and may seem to control the quality of excipients well, it may be impractical for the CFDA and most excipient manufacturers in China to implement it. For example, the mandatory requirement means that every excipient manufacturer has to follow this GMP, including the need to have costly cleanroom facilities (Table B) which are not the only means to prevent cross-contamination. Overall, the cost of production will increase significantly, making excipient manufacturing an unfeasible business and may force many manufacturers out of business, as extrapolated from the closure of many Chinese pharmaceutical companies when API GMP was made mandatory.[84] IPEC China had translated the IPEC-PQG GMP, along with the rest of the IPEC guides, in 2009 and submitted it to the CFDA.[85] It is highly recommended for CFDA to revise its excipient GMP to harmonize with the IPEC-PQG GMP. Moreover, the number of excipient manufacturers in China will prove to be a massive challenge for the CFDA and provincial

RAs	Details of Regulatory Controls for Excipients
European Medicines Agency (EMA) *(continued)*	Proposed EU GMP revisions:[56] • Risk-based selection and supervision of supply chain of excipients by FP manufacturers with appropriate aspects of production and control (e.g. handling, labelling, packaging and distribution requirements, complaints, recalls and rejection procedures) documented in quality agreements. • FP manufacturers shall establish supply chain traceability and audit suppliers for excipients with a particular risk to the quality of the FP. • FP manufacturers are responsible for testing starting materials. They may utilize partial or full test results from the approved starting material manufacturer, but the following must be fulfilled: - Signing of formal agreement between FP and starting material manufacturer, with special attention paid to distribution conditions to maintain the quality characteristics. - Auditing of testing sites of starting materials. - Certificate of analysis provided by the starting material manufacturer should be certified by a designated person with appropriate qualifications and experience. Starting materials certified to have been manufactured and checked for compliance with the requirements of the formal agreement. - Previous assessments of the supplier's excipients demonstrate a history of compliance. - Validation of supplier's certificate of analysis at appropriate intervals.
Indian Central Drugs Standard Control Organization (CDSCO)	FP manufacturers shall ensure that adequate arrangements are made for manufacture and supply of excipients.[57] Future development: • Schedule M shall be harmonized with WHO GMP for pharmaceutical products, which specifies better controls for excipients.[9,58]
United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA)	FP manufacturers shall:[59] • Comply with the principles and guidelines for starting materials set out in the GMP Directive. • Ensure that excipients are suitable for use by ascertaining that the appropriate level of EU GMP is applied in their manufacture. • Verify the authenticity and quality of any excipient to be used.
United States Food and Drug Administration (US FDA)	• Currently, there are no guidance that deals solely with the requirements of the excipient quality system.[35] • Every establishment involved in the manufacture of FPs, including excipient suppliers, shall be registered in an electronic database annually. They shall provide addresses, unique facility identifiers and, if applicable, names of US agents and importers for foreign establishments. • FP manufacturers shall include, as part of a drug listing, the names, addresses and unique facility identifiers (UFIs) of manufacturers of excipients used in their products. • FP manufacturers shall sample and test excipients for identity and for conformity with all appropriate written specifications for purity, strength, and quality.[60] • FP manufacturers shall implement quality oversight over their suppliers of excipients, including requirements set out by cGMP for FPs[39] • Registered establishments, both domestic and foreign, shall be subject to US FDA inspection, with a risk-based schedule. • US FDA shall exchange information with foreign RAs, inspect foreign establishments and allow foreign RAs to do likewise. • "Guidance for Industry: Testing of Glycerin for Diethylene Glycol"[61] recommended to FP manufacturers, where applicable.
Health Canada (HC)	• FP manufacturers shall sample each lot or container of excipients and fully test it against specifications, and conduct one specifically discriminating test for identity. • Sampling of a proportion of containers is permitted if the excipients come from a single product manufacturer, come directly from the manufacturer or if the manufacturer is accredited by regular audits by the FP manufacturer.[62]
Singapore Health Sciences Authority (HSA)	FP manufacturers shall: • Ensure that excipients are purchased only from approved suppliers. • Discuss manufacturing and quality specifications for the excipients with the suppliers. • Check containers of excipients for integrity of package and seal. • Check that the excipients' delivery invoice and labels match.[7] Excipient manufacturers and distributors shall adopt the guidelines set out in the Guidance Notes on Good Distribution Practice63 and adapt them specifically to their needs.

Table A (continued). Details of regulatory controls for excipients by various RAs.

FDA to inspect and ensure GMP compliance. The CFDA may not have the resources to regulate the excipient industry, due to the higher priority accorded to APIs and FPs.[50]

Assuring Supply Chain Integrity through Good Distribution Practices

Managing supply chain integrity involves minimizing risks that can arise anywhere along the supply chain, from the sourcing of the pharmaceutical raw materials to their use by the FP manufacturer.[27,86] Globalized excipient supply chains have become the norm for the 21st century pharmaceutical industry and have proven to be challenging for RAs and pharmaceutical companies to control or supervise, resulting in increased potential for adulterated excipients to enter the supply chain.[87] Without GDP compliance, the quality of excipients may deteriorate during the distribution phase due to unsuitable warehousing and transport conditions, cross contaminations, errors in labelling and in the traceability of lots.[5] The goal of GDP is to deter interference by opportunists and to provide effective means to detect adulterated products, thus preventing them from entering the supply chain.[86] All parties involved in the supply chain – brokers, traders, distributors, repackagers and other players, should implement GDP, commit to delivering pharmaceutical-grade excipients, and prevent interferences from happening.[27]

The WHO "Good Trade and Distribution Practices (GTDPs) for pharmaceutical starting materials document" outlines provisions that are applicable to all parties involved in handling pharmaceutical starting materials, including excipients. IPEC has published its GDP Guide for Pharmaceutical Excipients as an explanatory document to the WHO GTDP, by giving practical examples to facilitate the application of GDP specifically to pharmaceutical excipients. A matrix of applicability is provided in the IPEC Guide to help different excipient suppliers identify the sections of the WHO document that are applicable to their activities. The matrix differentiates warehousing and distribution activities from further processing activities, such as repackaging and relabeling activities. The IPEC Guide is, therefore, a useful tool for all distributors of the excipient supply chain. The WHO GTDP is currently being updated[88] with the IPEC Europe GDP committee working on revising the IPEC guide to align it with the proposed WHO revisions.[89]

The USP General Chapter <1197> Good Distribution Practices for Bulk Pharmaceutical Excipients provides general guidance about expectations of those involved in the supply and distribution of pharmaceutical excipients.90 However, information in this chapter is non-mandatory and serves only as a comprehensive reference for distributors and regulatory bodies.[90] In addition, General Chapter <1083> Good Distribution Practices—Supply Chain Integrity, which recommends practices for helping to ensure supply chain integrity for all drug components including excipients, is still in its draft form.[86,91-93] A review was conducted and overlaps were found among the current two chapters, <1197> and <1083>, and another chapter <1079> Good Storage and Shipping Practices. It was proposed by the USP Expert Committee to replace these three chapters with a series of new general chapters, as part of an overarching general chapter on GDP to eliminate overlaps, redundancies and inconsistencies among them.[93]

The FDASIA gives the US FDA more authority to tighten scrutiny on the pharmaceutical supply chain in general, with some legislations extending to excipients.[39,80] For example, the annual registration requirement for anyone involved in manufacture, preparation, propagation, compounding or processing of a drug (Table A) implies that excipient manufacturing facilities, both domestic and foreign, will be included as well.[80] This registration requirement, as well as

	CFDA GMP for Pharmaceutical Excipients	IPEC-PQG GMP for Pharmaceutical Excipients
Clean Room	Clean Room facilities are required to prevent cross contamination	Prerogative of manufacturer to decide how to implement measures to ensure excipient quality and avoid cross contamination.
Validation	• Validation Plan is required. • Specific requirements for process validation and cleaning validation.	• Full validation typically performed in pharmaceutical industry may not always be performed by excipient manufacturers. • Each process step should be controlled to the extent necessary to ensure that specifications are met • Validation should demonstrate the consistent operation of each manufacturing process
Risk Assessment	None included	Risk analysis is required to determine the processing step in which GMP should be implemented.
Shelf Life	Excipients are disallowed for use after their shelf life despite remaining within specification, resulting in unnecessary wastage of excipients which have exceeded their shelf life but are still found to be within specification.	Excipients can be used if found to remain within specifications after retest date.

Table B. Comparison of the CFDA GMP for Pharmaceutical Excipients and IPEC-PQG GMP for Pharmaceutical Excipients.

the need for FP manufacturers to provide the US FDA with the UFI of all of their excipient suppliers,[80] protects supply chain integrity by revealing all previous handlers of the excipients. It is unclear whether these listing requirements are extended to the excipient manufacturer's raw material suppliers and contract manufacturers or the identification of all manufacturing sites for each of the ingredients in excipient mixtures.[80] The FDASIA also allows the US FDA to inspect, by extension, excipient distributor facilities with risk-based frequencies, with the risk assessment methodology yet to be established.[80] The EU FMD is similar in this regard in allowing the RA of the respective EU or third country to inspect excipient importers - *Table A*.[40,82] However, these inspections are to be done only if there is suspected non-compliance to GDP,[40,82] and where there are no official standards prescribed for the import of excipients, indicating a gap in the legislation.

The CFDA's "Regulation of Strengthening Supervision on Pharmaceutical Excipients" (Table A) sets out similar requirements to those of the FDASIA, where FP manufacturers are required to submit the names of their excipient suppliers, as well as the audit results of the suppliers.[42] In addition, the CFDA's Regulation also stipulates a registry of credible pharmaceutical excipient manufacturers for FP manufacturers to select, be set up.[42] These measures help to secure the supply chain at the point of manufacture, but do little to regulate distribution from excipient manufacturers to users, allowing opportunists to interfere with the vulnerable supply chain. With China's history of excipient incidents,[16,17,28,29] the CFDA should include provisions for GDP compliance for all parties in the excipient supply chain in their regulation to ensure excipient pedigree.[83]

Harmonization and International Collaborations

The growing global supply chain setting has proven to be more difficult for RAs and pharmaceutical companies to control quality due to differing GMP and pharmacopoeial requirements, and inspection criteria among countries.[87] It is therefore necessary for RAs to cooperate as well as for GMP and GDP standards to be harmonized internationally in order to meet these challenges.

The role of the EMA involves harmonization of standards throughout the EU. It is involved in coordinating various activities like the preparation of new and revised guidance on these standards, advice on the interpretation of their requirements and related technical issues, as well as developing EU-wide procedures relating to inspections,[94] so that RAs within the EU cooperate and enforce the same standards within their respective countries. As the guidance for ascertaining the appropriate EU GMP for excipients is being drafted,[51] it is expected that this GMP will be harmonized among the countries in the EU.

Currently, most international collaborations focus on FPs and APIs,[95-101] and do not include excipients. For example, EMA has conducted two inspection programs with international partners, namely the joint initiative with the US FDA and the TGA on international GMP inspections of API manufacturers located outside the participating countries[102] and the EMA-US FDA joint inspection program for FP manufacturers.[103] An example of a Memorandum of Understanding (MOU) encompassing excipients is that between the US FDA and CFDA on the Safety of Drugs and Medical Devices.[104] Provisions in the MOU include regulatory cooperation by allowing US FDA inspections of excipient manufacturers and distributors in China and vice versa, as well as exchange of information like safety standards and inspection criteria.

International Pharmaceutical Excipients Councils

In recognition of the lack of global standards, the relevant RAs, and the excipient and pharmaceutical industries have formed the regional International Pharmaceutical Excipients Councils (IPECs), namely IPEC-Americas, IPEC-Europe, IPEC-Japan (JPEC) and IPEC-China, that make up the IPEC

Figure 6. Photographs of ExcipientFest, (a) Americas 2013[107] and (b) Asia 2013[108], seminars organised by IPEC to provide a forum for excipient users and manufacturers to share technical, regulatory, and commercial information.

Federation.[105] In addition, IPEC-India, the purported IPEC organization in the Indian Subcontinent, is expected to be registered as a formal trade association in 2014.[106] The key objectives of IPECs are the development and harmonization of international excipient standards, promotion of supply chain security, further development of third-party certification, while focusing on the applicable law, regulations, science and business practices, concerning pharmaceutical excipients of the respective regions. The IPECs have published many guidelines, programs and proposals on the various aspects of excipient control. These initiatives are designed to address specific needs related to excipient quality control.[38] The IPECs update the industry and RA representatives of these initiatives by conducting workshops and seminars (Figure 6) for them.[27]

Rx-360

The Rx-360 is a non-profit international supply chain consortium, comprising pharmaceutical companies, contract manufacturers, excipient suppliers, auditors and associations, such as the IPECs.[109] These bodies cooperate by sharing information and issuing standards, white papers and guidelines to enhance the pharmaceutical supply chain security.110 These documents help to assure the quality and authenticity of products moving through the supply chain, and hence protect patient safety.[111,112] Rx-360 actively engages the RAs and international organisations such as EMA, US FDA, WHO, EDQM, and PIC/S.[113]

The Pharmacopoeial Discussion Group and Harmonization of Pharmacopoeias

Excipient manufacturers which supply their products across the world have to perform different analytical procedures to ensure their products fulfil different pharmacopoeial requirements in the various regions. This is a burden that can be reduced with harmonized pharmacopoeial standards. The Pharmacopoeial Discussion Group (PDG) is made up of representatives of the European Pharmacopoeia, the Japanese Pharmacopoeia (JP), and the USP. The objective of the PDG is to harmonize pharmacopoeial standards, including excipient monographs, of the pharmacopoeias of the three regions. Currently, PDG meets twice a year and holds monthly status and technical teleconferences to advance harmonization work.[114] At present, 45 of the 62 excipient monographs on the work program[115] have been harmonized.[116]

Committees and technical working parties from the IPECs of America, Europe, and Japan have developed and proposed a number of excipient monographs identified by the major compendia as priority candidates for harmonization to PDG. Some of these submissions have been recommended for acceptance by one or more revision committees while others are under review by the pharmcopoeial committees.[68] The IPECs also hope to work with other global pharmacopoeias, such as the Indian Pharmacopoeia and Chinese Pharmacopoeia, to be more harmonized with the PDG pharmacopoeias. The IPECs can supply updated information on excipients as monographs are reviewed and revised.[38]

In May 2001, PDG welcomed the WHO as an observer.[114] With this arrangement, it had been proposed by the WHO Expert Committee on Specifications for Pharmaceutical Preparations that existing harmonized monographs, including excipients, should be included in the International Pharmacopoeia.[117] Despite this recommendation, none of the harmonized excipient monographs are on the working agenda for incorporation into the International Pharmacopoeia.[118] Only the harmonized general test methods[119] have been adapted to the editorial style of the International Pharmacopoeia and are included in the Third Supplement to the International Pharmacopoeia published in 2013.[120]

Recommendations to Improve Regulation of Excipients

Integration of IPEC Guidelines into Legislation

From the lack of official adoption of excipient standards and focus on only API and FP facility inspections in international RA collaborations, it is clear that excipients do not hold as much standing in importance as APIs and FPs in the regulatory paradigm. Without any regulatory or industrial guidance, the lack of harmonization among RAs' legislations creates confusion for excipient suppliers and their auditors, and provides loopholes for opportunists to exploit. Therefore, it is imperative that RAs work closely with the IPEC Federation, allowing the latter to advise on supervision of excipient quality and supply chain integrity. Doing so will also allow RAs to provide feedback on the IPEC guidelines, for example, loopholes or difficulties in enforcement for IPEC to revise and improve upon. Integrating IPEC guidelines into national legislations could be a first step toward harmonization of excipient regulation. Having common inspection criteria based on the IPEC GMP/GDP Audit Guides also could expedite international inspection of domestic and foreign excipient manufacturers, thus facilitating international cooperation.

It is forecasted that China and India will be spearheading the overall growth of the pharmaceutical excipients market with many American and European excipient manufacturers driven to invest and establish their subsidiaries in these regions to exploit the cheap manufacturing capabilities that these countries offer.[44,121] The absence of an Indian regulatory excipient framework, as well as the CFDA's skewed supervision of excipients, could undermine this economic advantage by failing to provide adequate assurance of excipient pedigree. The establishment of IPEC-India may be the way forward, where IPEC-India will guide the founding of the Indian regulatory charter through its guidelines while addressing issues of Indian excipient users and suppliers. In this way, the Indian excipient regulatory scene could be better harmo-

nized with that of the other IPEC countries, and regulatory cooperation with RAs like the US FDA and EMA may begin.

It is also hoped that CFDA revises its own excipient GMP to harmonize with that of the IPECs,[83] as well as consider other IPEC guidelines that IPEC-China had translated and submitted to CFDA for review. Doing so will put China on the same harmonized platform for excipient regulation with India, and will demonstrate China's commitment to better quality assurance of excipients internationally, while allowing Chinese manufacturers to do away with the requirements of the CFDA GMP for excipients, which have been perceived to be more expensive to implement.

Instead of drafting guidelines on the risk assessment for ascertaining the appropriate EU GMP for excipients,[51] the EMA could introduce IPEC guidelines with associated risk assessments to the FMD, even replacing the need to ascertain the appropriate EU GMP with dedicated excipient GMP. IPEC-Japan or JPEC could play a more integral role in working with the PMDA in incorporating IPEC guidelines to Japanese Law, replacing the voluntary JPEC GMP with the IPEC-PQG Guide.

In having to comply with the harmonized legislation of the RAs, manufacturers and distributors will not be confused with regard to which GMP or GDP standard to comply with and will have similar practices that will produce and deliver quality excipients that will not vary too much regardless of their sources.

Third-Party Supplier Audits

Currently, most RAs expect FP manufacturers to audit all their excipient suppliers. However, this is not possible due to practical constraints. It is unsustainable, especially for a big pharmaceutical company, to conduct on-site audits of every supplier on a regular basis.[122] It is also impractical, both logistically and economically, for excipient companies to host the multitude of audits from all their customers, direct and indirect.[27] Some RAs, like the US FDA,[39] EMA,[40] and CFDA[42] have even mandated inspection of manufacturers and distributors, which adds to the audit burden on the suppliers. This is also taxing on the regulators' resources,[50,123] considering the mandate to also inspect FP and API manufacturing and distributing facilities. In most cases, quality risk management is adopted instead.[39,40,42] Regulators like CFDA[50] and US FDA[124] are also exploring the use of third-party audits and certification to reduce the burden.

Third-party auditing and certification of excipient supplier reduce the audit/inspection burden for regulators as well as excipient users and suppliers.[50,122,125,126] Excipient suppliers are audited and their certificates or audit reports are made available for viewing to demonstrate effective implementation of GMP/GDP in their organization, so excipient customers and regulators need not inspect or audit the suppliers individually while suppliers host a single audit at appropriate frequencies.[127] Examples of comprehensive auditing schemes include the EXCiPACT™, International Pharmaceutical Excipients Auditing, Inc. (IPEA), and the Rx-360 audit programs.

EXCiPACT™ provides independent certification of excipient manufacturers and suppliers globally through EXCiPACT™-approved auditors, while minimizing the overall supply chain costs. EXCiPACT™ also publishes statistics about compliance of the global pharmaceutical excipients industry[127] - *Figure 7.* Audits are conducted using the EXCiPACT™ GMP and GDP standard, which is based on the IPEC GMP and GDP Guides without the parts already covered by ISO 9001:2008, which is harmonized and globally acceptable.[128] Suppliers have to be ISO-certified before EXCiPACT™ certification may apply.

Similar to EXCiPACT™, IPEA is another auditing scheme in which IPEA-approved auditors perform third-party audits of excipient manufacturers using the IPEC-PQG GMP Audit Guide. IPEA issues Excipient GMP Conformance certifications and audit reports to excipient manufacturers and distributors worldwide, which are made available to user companies throughout the industry.[38]

The two primary auditing programs of Rx-360 are the Joint Audit Program and the Audit Sharing Program.130 In the Joint Audit Program, audits are conducted by Rx-360-approved third-party auditors upon request from one or more Rx-360 member companies.[131] The audit is conducted pursuant to Rx-360 audit guidelines, based on the EXCiPACT™ Certification Standards.[132-133] Once an audit is completed, the audit report and documentation of the supplier's responses or corrective actions, redacting commer-

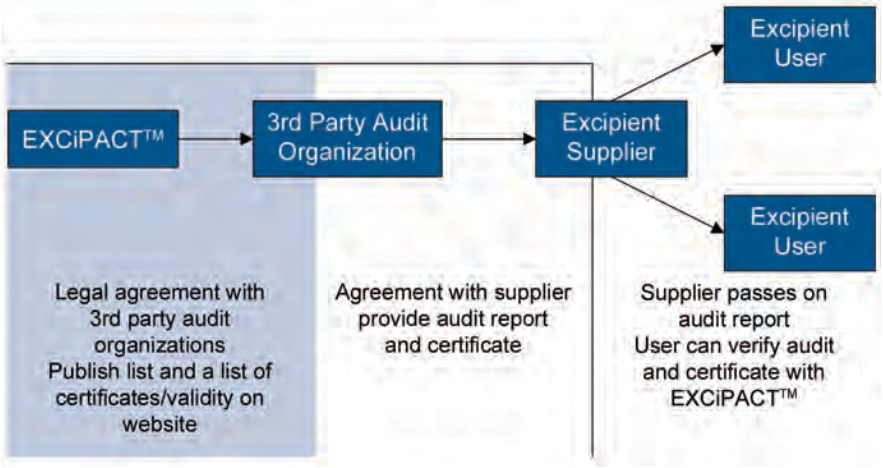

Figure 7. The EXCiPACT™ certification process.[129]

cially sensitive information, are made available on a secure Rx-360 database for the Audit Sharing Program.[134] It should be noted that an Rx-360 audit will not result in the awarding of any kind of Rx-360 certification or approval.[135]

Conclusion

With the global pharmaceutical excipient market expected to grow, and with the emergence of multifunctional and co-processed excipients,[121] the regulation of excipients will become more challenging. Currently, reported cases of adulterated excipients appear to be limited to DEG-laced glycerin and propylene glycol. However, as the excipient industry becomes more sophisticated and lucrative, motivation to profit unethically is expected to increase, and cases of other types of adulterated excipients may manifest.

Nationally, there is a lack of robust framework for excipient regulation. Internationally, the minimal collaboration and the lack of harmonization among regulators present loopholes in the excipient supply chain for opportunists to manipulate. Nonetheless, a more positive picture appears to come from the IPEC Federation and other established bodies, but they are, at best, self-imposed measures. The IPEC Federation could expand its reach to more countries, as it is doing with India, and cooperate more with regulators to integrate their Guides into legislations.

It is pertinent to note that stricter regulation comes with increased costs and other burdens. Suppliers will be faced with the decision of whether to continue supplying excipients, particularly those who do not supply to pharmaceutical customers as their core business. With their exodus, shortages in supply may lead to price inflation in capitalistic markets, where the temptation for economically-motivated adulteration is greater. In this regard, a tighter excipient regulatory framework should be implemented to prevent it from being counterproductive to its original intent.

Bearing in mind all these implications, it becomes apparent that there is a need to balance the interests of the different stakeholders when regulating excipients. As new regulatory initiatives and guidance emerge, only time will tell whether they are effective, and adjustments made accordingly to achieve a better control of the quality of pharmaceutical excipients and the supply chain integrity.

Acromyms

ANSI	American National Standard Institute
API	Active Pharmaceutical Ingredient
CDSCO	Central Drugs Standard Control Organization
CFDA	China Food and Drug Administration
cGMP	Current Good Manufacturing Practices
CP	Chinese Pharmacopoiea
DEG	Diethylene Glycol
EDQM	European Directorate for the Quality of Medicines

EMA	European Medicines Agency
EU	European Union
EU GMP	European Union Good Manufacturing Practices
FDASIA	Food and Drug Administration Safety and Innovation Act
FMD	Falsified Medicines Directive
FP	Finished Product
GDP	Good Distribution Practices
GMP	Good Manufacturing Practices
GTDP	Good Trade and Distribution Practices
HC	Health Canada
HSA	Health Sciences Authority
IPEA	International Pharmaceutical Excipients Auditing, Inc.
IPEC	International Pharmaceutical Excipients Council
ISO	International Organization for Standardization
JP	Japanese Pharmacopoeia
JPEC	Japan Pharmaceutical Excipients Council or IPEC-Japan
MHRA	Medicines and Healthcare Products Regulatory Agency
MOU	Memorandum of Understanding
NTTA	National Technology Transfer and Advancement Act
PDG	Pharmacopoeial Discussion Group
Ph.Eur	European Pharmacopoeia
PIC/S	Pharmaceutical Inspection Convention/ Co-operation Scheme
PMDA	Pharmaceutical and Medical Devices Agency
PQG	Pharmaceutical Quality Group
QC	Quality Control
RA	Regulatory Authority
SFDA	State Food and Drug Administration
TGA	Therapeutic Goods Administration
UFI	Unique Facility Identifiers
UK	United Kingdom
US	United States
US FDA	United States America Food and Drug Administration
USP	United States Pharmacopoeia
WHO	World Health Organization
WHO GMP	World Health Organization Good Manufacturing Practices

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Editor's Note: please visit www.pharmaceuticalengineering.org to view the References, in their entirety.

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Standardized Extractables Testing Protocol for Single-Use Systems in Biomanufacturing

by Weibing Ding, Gary Madsen, Ekta Mahajan, Seamus O'Connor, and Ken Wong

This article presents a concensus standardized extractables testing protocol for single-use systems in biomanufacturing.

The Need

General requirements for Extractables and Leachables (E&L) are already mandated by regulatory agencies.[1-2] Biopharmaceutical companies must meet these requirements in demonstrating equipment suitability and GMP compliance whether the equipment is of traditional design or single-use. However, because of the absence of specific regulatory requirements for extractables testing of Single-Use Systems (SUS) components, companies have needed to generate SUS extractables testing methods by extrapolating from their interpretation of regulatory requirements for existing container closure testing methods.

Extractables testing studies conducted by suppliers of SUS for biomanufacturing comprise filling or soaking SUS components in model solvents, and testing the resultant extracts for compounds that were released to the solvent by the treatment. Exposure times and temperature ranges are extended to exaggerate the chemical conditions of actual use. However, there are currently no industry standards for such studies, and while solvents used are often more aggressive than what is typical in biomanufacturing, the full range of conditions encountered by SUS components in actual use is not always represented. In addition, this lack of standardization in extractables testing creates difficulties for end-users in interpreting and comparing test data from different SUS suppliers.

Extractables testing study data provided by SUS suppliers must be well documented, reproducible, and readily interpretable in order for biopharmaceutical companies to use a scientific and risk-based approach in determining the readiness of various submissions to regulatory agencies. Current regulatory guidance[1-2] requires that biopharmaceutical manufacturers ensure the manufacturing systems do not adulterate the final drug product. The end users have used SUS extractables testing data and leachables evaluation to assess potential risks to patients of the use of these components in product manufacturing. If extractables testing data provided by an SUS supplier are not sufficient to perform adequate assessment of risks, it is the time-consuming process for the biopharmaceutical company to conduct their own studies to generate sufficient extractables testing data. This results in the same components being tested multiple times and delay in applications of SUS in biomanufacturing.

For a biopharmaceutical company to move a new drug molecule candidate through the clinical development process, the company first develops a position on the drug candidate that will be presented to regulatory agencies for concurrence. This position is applied to successive stages of the clinical development process, culminating in final process validation for commercial manufacturing and licensure. Regulatory guidance for Process Validation outlines three distinct stages: process design, process qualification, and process verification.[3] Equipment design data for bioprocessing components, whether of traditional or single-use design, is required at each stage. Extractables testing is a key

element of SUS equipment design. Reviewing data derived from extractables testing is the mechanism by which SUS suppliers ensure safety of the polymers used in fabrication of their products. This data is also the best means for end-users to evaluate fitness of a given SUS component for use in their specific biomanufacturing processes.

SUS technology has numerous advantages for improving cycle time of biopharmaceutical products and in reducing overall manufacturing costs. Because it is in the interest of SUS suppliers, SUS end users, and patients in need of the biopharmaceutical products to accelerate the implementation of SUS components within the biopharmaceutical industry, a standardized extractables testing protocol with an agreed-upon set of testing methods to generate and analyze extracts is needed to establish common expectations among suppliers, end-users, and regulators on the type of extractables testing data to be generated.[4] The benefits of such standardization would include not only an enhanced ability of end-users to make informed choices when comparing SUS components from various suppliers, but also would assist SUS suppliers in more efficiently selecting materials in line with end-user needs and in controlling product variability.

BioPhorum Operations Group Extractables Work Group Proposal

The proposal outlining standardized methods for extractables testing of SUS components contained in this article was developed by the Extractables Work Group of the BioPhorum Operations Group (BPOG) and is based on results of a survey of 17 major BPOG member companies across 26 sites. As such, these recommendations reflect the broad SUS applications of end-users at biopharmaceutical organizations that produce a diversity of biologic products in a variety of regulatory environments. The protocol covers the methods used for extractables testing studies, including sample preparation, extraction conditions, recording test article sampling conditions, and reporting data from analysis of extracts.

Integration of these proposals by SUS suppliers into their existing product lifecycle management processes would be highly beneficial to suppliers to ensure that a comprehensive and consistent set of extractables testing data are readily available to biopharmaceutical end-users. A draft of the proposal was previously provided to 10 SUS equipment suppliers and 10 contract analytical testing laboratories for feedback on the methods proposed. Each responding organization was encouraged to provide both a written response as well as to participate in discussion forums with members of the BPOG Extractables Work Group.

Application of the Extractables Data

The extractables testing information package to be provided by an SUS supplier is not intended to be passed directly to

a regulatory agency without a process- and product-specific evaluation. Rather, the purpose of the information package is to allow the SUS end-user to rigorously estimate the types and amounts of leachables that will be generated by the SUS component during its intended bioprocessing use in order to assess risks to patient safety and to demonstrate product compatibility, process performance, and fitness of the functional design for its intended purpose.[5-16] The use of standardized protocols also provides a baseline which can be used for comparative assessments of SUS from different suppliers as back-ups or alternate sources. Such an approach greatly facilitates the long-term success of SUS for biopharmaceutical manufacturing.

Note: the final responsibility for confirming the safety and efficacy of a healthcare product remains that of the end user, who should take a science and risk-based approach to determining what additional studies should be conducted based on the application, point and phase of use.

Scope

This BPOG's standardized extractables testing protocol applies, but is not limited, to the following SUS components that come into contact with product or process fluids. The standardized extractables testing protocol does not cover final container closure systems.

- Bags and films used for storage, mixing, or as bioreactors
- Tubing
- Tubing connectors and disconnectors
- Aseptic connectors and disconnectors
- Sterilizing-grade and process filters
- Tangential flow filtration cassettes
- Sensors
- Valves
- Elastomeric parts (gaskets, O-rings, diaphragms, and septum)
- Wetted polymeric surfaces of positive displacement pumps
- Chromatography columns
- Molded parts of mixers (e.g., impellers)
- Filling needles

A supplier of SUS assemblies is not required to generate extractables data for SUS components not manufactured by them as long as the assembly supplier provides end-users with data from the actual manufacturer of the component that complies with the standardized extractables testing protocol.

Extractables Studies

Methods applied in SUS extractables studies are specific to each category of SUS components. One key aspect of extractables testing studies is ensuring that the SUS component is exposed to a volume of solvent sufficient to effectively model what occurs during use of the component in actual biomanufacturing processes. For the majority of components, the ratio of a sample's surface area to the volume (cm^2/mL) of solvent to which it is exposed during testing should be maintained at 6:1 or greater.[17] One important exception to this rule involves filters, for which the ratio of effective filtration area to solvent volume (cm^2/mL) should be maintained at 1:1 or better. For any other SUS components for which the 6:1 (cm^2/mL) Surface Area to Volume ratio (SA/V) standard cannot be achieved, exposure of component surface area to solvent volume ratio should be maximized. In these exceptional cases, the final component surface area to solvent volume ratio arrived at should be justifiable based on the component's intended use.

When performing extractables testing, the sample extraction setups listed in Table A for the various SUS component types are used. Extraction solvents, exposure times, and exposure temperatures by SUS component type are listed in Table B. The proposed study conditions along with the following instructions should be adhered to as closely as is practical.

- Negative controls to calculate background levels should be included for all tests, using the same test setup minus the test article. For negative control, polytetrafluoroethylene (PTFE) bottles are recommended for inorganic elemental analysis, while validated or qualified clean glass bottles are suitable for organic analysis.
- If an item is pre-treated prior to actual use, the item should be pre-treated the same way before being used in extractables testing. For example, extractables testing results for a gamma-irradiated component cannot be used to represent the results of the same component after autoclaving.
- If the SUS component is intended for use after gamma irradiation, a gamma-irradiated test article should be used for the extraction study. The test article should be irradiated to attain a minimum dose within 10 kGy of the maximum-allowed dose (e.g., 45 to 55 kGy, if the maximum-allowed dose is 55 kGy). The irradiation facility (i.e,. irradiator design, equipment, and process) used should be validated according to ANSI/AAMI/ISO 11137-1:2006 and ANSI/AAMI/ISO 11137-3:2006. Due to the fact of degasing of volatile organic compounds from the gamma-irradiated components, the time between the gamma irradiation and the extraction test should be five weeks to represent the typical worst case production scenario.
- If the component is intended for use after autoclaving, an autoclaved test article should be used for extraction study. The test article should be autoclaved according to the component product claim. The time between the

autoclaving and the extraction test should be within 24 hours or as soon as practical. If the component can be either gamma-irradiated or autoclaved, separate studies for each condition should be performed.

- At least two samples of a component should be tested for extractables, each from different production lot.
- When recirculation methods are used in extractables testing on filters, inert materials such as PTFE should be used for surfaces of pumps, tubing, and other components of the fluid supply system that contact recirculating fluids.
- During the extraction, part of the test solvent may evaporate. For this reason, the starting and end volume of the test solvent should be recorded. These values may be used in calculations for correction of analytical results, where appropriate.

Choice of Extraction Solvents, Exposure Times, and Exposure Temperatures

Testing SUS components with the solvents, exposure times, and exposure temperatures listed in Table B will provide extractables data applicable to most biomanufacturing processes. Unique solvents and process conditions have been excluded. Solvents, exposure times, and exposure temperatures are recommended that represent reasonable worst-case conditions for most typical biomanufacturing applications. The initial time point at Time 0 (≤ 30 minutes) is based on well accepted analytical practices and sets a baseline for extraction kinetics evaluation. Studies have shown that the amount of some volatile extractable compounds decreased over time from Time 0 to 24 hours.[24] It is also critical for cell viability assessment as volatile leachable compounds from bags come in direct

Storage, Mixing, or Bioreactor Bags and Films
• Use a bag of size sufficient to provide an adequate volume of extract for analysis but ≤ 5L • Record the volume of the bag • Fill the bag with a volume of solvent sufficient to maintain 6:1 (cm^2/mL) surface area to volume (SA/V) ratio • Place on an orbital or rocker shaker at a minimum of 50 rpm[a] for the test time period • Record the solvent and concentration used, extraction time, and temperature (Table B) • Express analytical results in µg/cm^2 Note: Studies performed on 2D bags of same materials can represent other bag designs, e.g., 3D bags
Tubing
• Use a sufficient length of ½" ID (inner diameter) tubing to provide an adequate volume of extract for analysis • Record the total length and ID of tubing • Fill the tubing with a volume of solvent sufficient to maintain 6:1 (cm^2/mL) SA/V ratio • Use pinch clamps (or equivalent) to close the ends • Place on orbital shaker at a minimum of 50 rpm for the test time period • Record solvent and concentration used, extraction time, and temperature (Table B) • Express analytical results in µg/cm and µg/cm^2
Tubing Connectors or Disconnectors
• Use a sufficient number of ½" ID connectors or disconnectors to provide adequate volume of extract for analysis • Record length and ID of each connector • Submerge in a volume of solvent sufficient to maintain 6:1 (cm^2/mL) SA/V ratio • Place on orbital shaker at a minimum of 50 rpm for the test time period • Record the solvent and concentration used, extraction time, and temperature (Table B) • Express analytical results in µg/cm^2 and µg/unit
Aseptic Connectors or Disconnectors
• Use a sufficient number of ½" ID connectors or disconnectors to provide an adequate volume of extract for analysis • Multiple connectors can be used and extracts pooled for analysis • Record the length and ID of each connector • Fill the connectors or disconnectors with a volume of solvent sufficient to maintain 6:1 (cm^2/mL) SA/V ratio • Use PTFE caps (or equivalent inert materials) to close ends of connectors or disconnectors • Place on an orbital shaker at a minimum of 50 rpm for the test time period • Record the solvent and concentration used, extraction time, and temperature (Table B) • Express analytical results in µg/cm^2 and µg/unit
Sterilizing-grade and Process Filters
• Use filters with Effective Filtration Area (EFA) ≥ 0.1 m^2 • Record the EFA of filter • Recirculate or fill with a volume of solvent sufficient to maintain 1:1 (cm^2/mL) EFA to volume ratio • If the solvent is not recirculated through the filter, place the filter filled with test solvent on an orbital shaker at a minimum of 50 rpm for the test time period. Record the solvent and concentration used, extraction time, and temperature (Table B) • Express analytical results in µg/cm^2 of EFA and µg/unit
Tangential-flow Filtration Cassettes
• Use cassettes with an EFA ≥ 0.1 m^2 • Record EFA of cassette • Recirculate volume of solvent sufficient to maintain 1:1 (cm^2/mL) EFA to volume ratio • Any required preflush, sanitization, or flush steps should be performed prior to extraction • Record solvent and concentration used, extraction time, and temperature (Table B) • Express analytical results in µg/cm^2 of EFA and µg/unit
Sensors or Valves
• Use a sufficient number of ½" ID sensors or valves to provide an adequate volume of extract for analysis • Multiple sensors or valves can be used and extracts pooled for analytical purpose • Record the total surface area as the sum of tube and functional sensor surfaces for sensors; record the total surface area as the sum of valve diaphragm and tube surfaces for valves • Fill the sensor set or valve with a volume of solvent sufficient to maintain 6:1 (cm^2/mL) SA/V ratio or closest possible SA/V ratio • Use PTFE caps (or equivalent inert material) to close ends of tubes of sensor or valve • Place on an orbital shaker at a minimum of 50 rpm for the test time period • Record the solvent and concentration used, extraction time, and temperature (Table B) • Express analytical results in µg/sensor or µg/valve, and µg/cm^2
Chromatography Columns or Molded Parts of Mixers or Elastomeric Parts (gaskets, O-rings, diaphragms, and septum) or Wetted Polymeric Surfaces of Positive Displacement Pumps
• Use a sufficient size of coupon representing the finished column or molded parts of the mixer or elastomeric parts (gaskets, O-rings, diaphragms, and septum) to provide an adequate volume of extract for analysis • Record the total surface area of the coupon • Submerge the coupon in a volume of solvent sufficient to maintain 6:1 (cm^2/mL) SA/V ratio • Place on an orbital shaker at a minimum of 50 rpm for the test time period • Record the solvent and concentration used, extraction time, and temperature (Table B) • Express analytical results in µg/cm^2
Filling Needles
• Use needles with smallest ID available • Record the inner diameter and total surface area of the needle • Submerge needles in a volume of solvent sufficient to maintain 6:1 (cm^2/mL) SA/V ratio or closest possible SA/V ratio • Place on an orbital shaker at a minimum of 50 rpm for the test time period • Record the solvent and concentration used, extraction time, and temperature (Table B) • Express analytical results in µg/cm^2
Abbreviation: rpm = revolutions per minute or rocks per minute — [a] 50 rpm at 20 mm radius

Table A. Testing setup for various SUS components.

contact with process fluid immediately which can impact cell culture processes.[13] Protein stability can be impacted by change of pH or interaction of protein solutions with volatile and/or semivolatile leachable compounds on immediate contact. The 70-day data point specified for the storage bags and tubing is necessary to support long term storage of up to three years shelf life at 0°C storage condition. Tubing was included simply because tubing sections are typically integrated to the bag during storage. The combination of the temperature and time was established based on the ASTM F1980-07 Standard Guide for Accelerated Aging of Sterile Medical Devices.[18]

The common extraction model solvents included here comprise a broad range of buffer-based process fluids: Water For Injection (WFI), 0.1M phosphoric acid (low pH), and 0.5N NaOH (high pH). The choice of 50% ethanol was selected to represent organic solvents commonly used in bioprocesses such as aliphatic alcohols and glycols. Typical surfactant-containing aqueous solutions are represented by 1% Polysorbate-80. Polysorbate-80, even at very low concentration, facilitates the leaching of small-molecule, aromatic compounds.[25] The model solvent chosen to represent high salt concentrations in bioprocessing was 5M NaCl (high ionic strength). A review of available data packages and publications from SUS suppliers and end users indicated that certain chemicals observed in a NaCl extract were not detected in WFI extract.[6,19] In other cases, the same extractables were observed in both NaCl and WFI extracts, but at significantly higher concentrations in the former. The six solvents also effectively simulate protein solutions which typically involve high pH, low pH, salt, WFI, organic compound and surfactant.

The base and acid recommendations cover most pH ranges in user operational conditions. When the recommended pH range is outside of the single-use component's product claim due to chemical compatibility issue (e.g., polycarbonate-based aseptic connector is not compatible with 0.5N NaOH), the compatible pH range should be used for the testing and the justification should be stated in the Summary Extractables Statement.

	Solvents						Time				
	50% Ethanol	1% PS-80	5M NaCl	0.5N NaOH	0.1 M Phosphoric acid	WFI[a]	Time 0 (≤ 30 min)	24 hours	7 days	21 days	70 days
							Temperature				
							Ambient (25°C)	40°C			
Storage, Mixing, and Bioreactor Bags	X	X	X	X	X	X	X	X		X	X[b]
Tubing	X	X	X	X	X	X	X	X		X	X[b,c]
Tubing Connectors and Disconnectors	X	X	X	X	X	X	X	X		X	
Aseptic Connectors and Disconnectors	X	X	X	X	X	X	X	X	X		
Sterilizing-grade Filters/Process Filters	X	X	X	X	X	X	X	X	X		
Tangential-flow Filtration Cassettes	X	X	X	X	X	X	X	X		X	
Sensors and Valves	X	X	X	X	X	X	X	X		X[d]	
Chromatography Columns; Elastomeric Parts (gaskets, O-rings, diaphragms, and septum); Wetted Polymeric Surfaces of Positive Displacement Pumps	X	X	X	X	X	X	X	X			
Molded Parts of Mixers	X	X	X	X	X	X	X	X		X	
Filling Needles	X	X	X	X	X	X	X	X			

Abbreviations: PS-80 = Polysorbate-80; WFI = water for injection; min = minute.
[a] Deionized water can be used for this purpose if WFI is not available.
[b] Duration, specified for testing storage bags and tubing, is necessary to support 3-year storage time at 0°C.
[c] Tubing is included because tubing sections are typically integrated with bags during storage.
[d] The 21-day time-point applies only to sensors used with bioreactors (e.g. for dissolved oxygen and pH).

Table B. Extraction solvents, exposure times, and exposure temperatures by SUS component type.

Analytical Techniques

The goal of the analytical techniques used in extractables testing is to identify and quantitatively assess compounds resulting from the extraction of SUS components. The results can then be used for safety assessments.[20] In cases where quantitation is not possible, semi-quantitative values should be reported. Extracts referenced in this section on analytical techniques are the solutions generated by the use of solvents on SUS components during extractables testing studies.

The analytical techniques proposed in this article were selected to detect the widest possible range of chemical compounds. An individual compound detected at a concentration of 0.1 µg/mL or greater should be identified, confirmed and quantified by use of an authentic reference compound (e.g., extractables known to result from component raw materials). Compounds observed at a concentration below 0.1 µg/mL should be identified by mass spectral library match and confirmed with quantitation if an authentic reference compound is available. When an authentic reference compound is not available, a chemically similar compound may be used although this will result in semi-quantitative values in the results. (See Appendix: Recommended Analytical Techniques for Extractables Identification and Quantification).

Analysis by High Performance Liquid Chromatography (HPLC) or Ultra-High Performance Liquid Chromatography (UHPLC) coupled with Photodiode Array (PDA) detection and Mass Spectrometry (MS) is required for all extractables testing. It is acknowledged that certain extraction solvents may present challenges in detection (i.e., PS-80 extracts). Dilution of the extracts to acceptable matrix interference concentrations is acceptable in these cases (e.g., 0.1% PS-80).

Mass spectrometric analysis should be conducted in both positive and negative mode with Electrospray Ionization (ESI) as well as Atmospheric Pressure Chemical Ionization (APCI) techniques. Use of two ionization methods provides complementary data and allows detection of the maximum range of potential extractable compounds resulting not only from bulk component material, but from additives and degradation products as well.

Gas Chromatography (GC) with headspace inlets for volatiles and direct injection inlets for semi-volatiles is also required for all extractables testing. Mass spectrometric detection should be performed in conjunction with either technique to permit compound identification via mass spectral libraries. Alternate detectors (e.g., nitrogen phosphorus, flame ionization, or nitrogen chemiluminescence) for specific classes of compounds may be used in addition to MS detection if required due to the nature of the specific component materials and potential extractables involved.

Inductively-Coupled Plasma Mass Spectrometry (ICP-MS) also should be performed to detect and quantify extractable metals. Optical Emission Spectroscopy (OES) as an alternate detection method may be used provided specificity and required detection limits can be achieved. Extracts should be analyzed intact unless dilution of the samples allows the required detection limits to be met for all metals of interest. In cases where the extract matrix would produce known interferences in detecting particular metals, a different isotope should be selected to minimize the interference. At a minimum, the amounts of all metals appearing in extracts that are specified in USP <232>,[21] EMEA,[22] and ICH guidelines[23] should be quantified and reported. While it is only required to record results from the final extractables testing time point, additional time points may be analyzed as necessary.

The detected and identified compounds should be named based on International Union of Pure and Applied Chemistry (IUPAC) nomenclature, and reported with Chemical Abstracts Service (CAS) registry number, empirical formulas, chemical structures, and molecular weights, when possible.

Additional analytical techniques should be used to supplement the required data, in particular, to determine the Total Organic Carbon (TOC) and pH of extracts when the test solvent does not interfere. Non-volatile residue determination may be necessary in addition to the required analytical techniques when the test solvent is volatile. Resulting extractables testing data should be compiled into an extractables test report with representative chromatograms and raw data tables of the results. The extractables test report should include the amount and identity of known compounds and the estimated amount and class of compound for unknowns. The extractables test report also should include the analytical conditions for each technique as well as any additional discussion necessary to provide enough context such that the results are readily interpretable by end-users. Specific analytical parameters and method sensitivity criteria are presented in the Appendix.

Extractables Test Report

This standardized extractables testing protocol provides suppliers with a set of procedures agreed upon as representative of a comprehensive range of conditions by a broad group of companies. Suppliers can then prepare standardized extractables test reports for SUS components, including, but not limited to, bags and films, tubing, tubing connectors and disconnectors, aseptic connectors and disconnectors, sterilizing-grade and process filters, tangential-flow filter cassettes, sensors, valves, chromatography columns, molded parts of mixers, and filling needles. The extractables test report provides comprehensive information on the SUS component tested, including materials of construction, details of the testing setup, testing conditions and analytical methods applied, and identity and quantity of extracted compounds. The extractables test report should include the following in-

formation for each extractables study:

1. **Summary Extractables Statement**

   The summary extractables statement for SUS components tested should consist of:
   a. Summary of the materials of construction
   b. Testing setup
   c. Extraction conditions applied
   d. Analytical methods applied
   e. Identity and quantity of extracted compounds (analytical results)

2. **Details of pre-treatment methods**

   a. Gamma irradiation description includes the minimum and maximum dose allowed for the component during the manufacturing process and the actual dose used to gamma irradiate the component for testing.
   b. Autoclave description should include time (total and exposure) and temperature of each autoclave cycle. If multiple cycles are performed, the number of cycles also should be specified.
   c. Pre-flush description includes flush fluid used, temperature, time, and flush volume. Pre-flush typically applies to components such as tangential flow filtration cassettes.

3. **Time intervals between manufacture, irradiation, and testing for gamma-irradiated bag films**

   The time interval between when a bag film is manufactured and when gamma irradiation is applied should be recorded. The additives in polymers used to make bag films can oxidize over time, and the oxidized additives can generate different extractables compared to virgin additives. The time interval

Test Article			
Number of Test Articles			
Part Number			
Lot Numbers			
Pretreatment[a]	Variable(s)	Units	Value(s)
Gamma irradiation	Dose	kGy	
Autoclave	Time, temperature, number of cycles	minutes, °C, #	
Pre-flush	Fluid identity, duration, temperature, volume	Name, minutes, °C, L	
Test Article Extraction Conditions	Variable	Units	Value(s)
	Temperature	°C	
	Duration	Minutes, hours, days	
	Solvent contact surface area	cm^2	
	Solvent volume	mL	
	Surface area to volume ratio	ratio	
Supporting Information			
Bags	Film thickness	mm	
	Volume (capacity)	L	
Tubing	Wall thickness	mm	
	Internal diameter	mm	
	Length	mm	
Tubing connectors and aseptic connectors	Internal diameter	mm	
	Length	mm	
Filters and TFF cassettes	EFA	m^2	
Filling needles	Internal diameter	mm	
2D and 3D bags	Time between film manufacturing and gamma irradiation	Days (Lot 1) Days (Lot 2) Days (Lot 3), if applicable	
All gamma-irradiated components	Time between gamma irradiation and extraction	days	
	Typical dose range during normal manufacturing	kGy	

Abbreviations: EFA = effective filtration area; TFF = tangential flow filtration.
[a] If none, indicate N/A (not applicable).

Table C. Information to be reported in summary extractables statement.

between gamma irradiation and extraction also should be reported.

4. Thickness of the bag films and tubing

Multiple thicknesses of bag films are often available, e.g., 0.05 mm, 0.15 mm, and 0.5 mm. The thickness of the bag film or tubing should be reported.

5. Composition of fluid-contacting surface materials

Materials comprising the surfaces that contact test solvents during testing, e.g., the inner surface of tubing or connectors, the interior of bioprocess bags as well materials of construction of other layers, or the fluid-contacting components of filters, should be specified.

6. Traceability of components

The part numbers and lot numbers of test articles should be reported. These numbers should be traceable back to the lot numbers of resins used in manufacturing of the tested component.

For each extractables study, the following information in Table C is recorded and included in each summary extractables statement. Results of extract analysis (compound identities and amounts) are recorded separately.

Next Steps

The companies involved in the BPOG Extractables Work Group encourage the adoption by all SUS suppliers of the recommendations made in this article. Not only will adoption enable results from extractables testing on SUS components to be compared and used by SUS integrators and end-users, but also will simplify the approach of SUS suppliers to serve their markets. Such standardization will provide a set of common expectations for SUS component performance that SUS end-users, SUS suppliers, and regulators can reference as the current good extractables testing practice.

This standardized extractables testing protocol also will be made available to standard-setting organizations, such as ASTM and USP for consideration in developing a consensus standard. We expect that once a consensus standard has been agreed upon that a transition plan will be created with reasonable timeframes permitting suppliers to bridge any existing gaps between the new standard and their existing extractables testing and documentation procedures.

Appendix: Recommended Analytical Techniques for Extractables Identification and Quantification

Outlined below are the recommended approaches for the four major analytical techniques applied to the identification and quantification of extractables from SUS components.

1. Detection of Extracts by LC-UV-MS: HPLC with UV Photodiode Array Detection and Mass Spectrometry

Standards	Bisphenol A (BPA) and Irganox® 1010a (method sensitivity and range)
Limit of Detection	BPA, standard signal-to-noise ratio ≥ 3
Precision (UV)	1 ppm BPA, RSD ≤ 20% (n = 6)
Spike Recovery (UV)	80 - 120%
Column	C18
Mobile Phase A	Acidified water
Mobile Phase B	Organic (ACN and/or acidified MeOH)
PDA range	200 to 400 nm

Abbreviations: LC = liquid chromatography, MS = mass spectrometry, HPLC = high performance liquid chromatography, UV = ultraviolet, RSD = relative standard deviation, ACN = acetonitrile, MeOH = methanol
[a] Irganox is registered trademark of Ciba Specialty Chemical Corporation

Table D. Assay performance parameters for HPLC with UV photodiode array and mass detection.

Notes:

- Other chromatographic instrumentation, such as Ultra-High Performance Liquid Chromatography (UHPLC) and conditions may be used to meet assay performance parameters.
- Limit of Quantitation (LOQ) should be reported.
- Standards listed in the table are to demonstrate method sensitivity and chromatographic range. Additional known extractable compounds should be prepared as standards injected for each unique material.
- An injection of standard should occur at least once for every 10 sample injections.
- Spike is 1 ppm BPA in water and in 50% water/50% ethanol.
- Control sample injections should be run to subtract matrix-associated peaks from consideration.
- Report levels of peaks from samples that are also observed in controls ≥ 50% higher than in controls.
- Mass spectrometric detection is both +/- Electrospray Ionization (ESI) and Atmospheric Pressure Chemical Ionization (APCI).
- Mass spectrometric detection scan range is 100 to 2000 m/z.
- In cases where quantitation is not possible, semi-quantitative values may be reported by reference to responses of suitable standards.
- For semi-quantitative analysis, results for peaks with a signal-to-noise ratio > 10 or peaks above area of lowest standard injection should be reported.

2. Detection of Extracts by GC-MS: Direct Injection Gas Chromatography with Mass Spectrometry

Standards	n-Octane and butylated hydroxytoluene (method sensitivity and range)
Limit of Detection	BHT, standard signal-to-noise ratio ≥ 3
Precision (TIC)	1 ppm BHT, RSD ≤ 20% (n = 6);
Spike Recovery (TIC)	80 - 120%
Column	DB-5MS (or equivalent)
Abbreviations: GC = gas chromatography, TIC = total ion current, BHT = butylated hydroxytoluene, RSD = relative standard deviation	

Table E. Assay performance parameters for direct injection GC with mass detection.

Notes:

- Other chromatographic instrumentation and conditions may be used to meet assay performance parameters.
- Chromatographic data should be presented using the Total Ion Current (TIC).
- Limit of Quantitation (LOQ) should be reported.
- Standards listed in the table are to demonstrate method sensitivity and chromatographic range. Additional known extractable compounds should be prepared as standards injected for each unique material.
- An injection of standard should occur at least once for every 10 sample injections.
- Spike is 1 ppm BHT in water and in 1% Polysorbate-80 extraction solvent.
- Control sample injections should be run to subtract matrix-associated peaks from consideration.
- Report levels of peaks from samples that are also observed in controls ≥ 50% higher than in controls.
- Mass spectrometric detection scan range is 30 to 600 m/z.
- In cases where quantitation is not possible, semi-quantitative values may be reported by reference to responses of suitable standards.
- For semi-quantitative analysis, results for peaks with a signal-to-noise ratio > 10 or peaks above area of lowest standard injection should be reported.

Liquid-Liquid Extraction Procedure for Direct Injection

- Use Dichloromethane (DCM) as an extraction solvent and phenanthrene-d10 as an internal standard.
- Adjust pH as needed.
- Extract aqueous samples in 1:1 (v/v) ratio with DCM, including internal standard; repeat extraction three times on each aqueous sample aliquot.
- Combine DCM fractions and evaporate to approximately 1 mL; repeat preparation if sample reaches significantly less than 1 mL.
- Reconstitute concentrated extract for analysis with DCM to final volume equal to original sample aliquot volume.

3. Detection of Extracts by GC-MS: Headspace Sampling GC with Mass Spectrometry

Standards	Methanol, MEK and octamethylcyclotetrasiloxane (method sensitivity and range)
Internal Standard	Toluene-d_8
Limit of Detection	MEK, standard signal-to-noise ratio ≥ 3
Precision (TIC)	1 ppm MEK, RSD ≤ 20% (n = 6)
Spike Recovery (TIC)	70 - 130%
Column	DB-624 (or equivalent)
Abbreviations: MEK = methylethyl ketone, RSD = relative standard deviation, TIC = total ion current	

Table F. Assay performance parameters for headspace sampling GC with mass detection.

Notes:

- Other chromatographic instrumentation and conditions may be used to meet assay performance parameters.
- Chromatographic data should be presented using the Total Ion Current (TIC).
- Limit of Quantitation (LOQ) should be reported.
- Standards listed in the table are to demonstrate method sensitivity and chromatographic range. Additional known extractable compounds should be prepared as standards injected for each unique material.
- An injection of standard should occur at least once for every 10 sample injections.
- Spike is 1 ppm MEK in water and in 1% Polysorbate-80 extraction solvent.
- Control sample injections should be run to subtract matrix-associated peaks from consideration.
- Report levels of peaks from samples that are also observed in controls ≥ 50% higher than in controls.
- Mass spectrometric detection scan range is 30 to 400 m/z.
- In cases where quantitation is not possible, semi-quantitative values may be reported by reference to responses of suitable standards.
- For semi-quantitative analysis, results for peaks with a signal-to-noise ratio > 10 or peaks above area of lowest standard injection should be reported.

4. Detection of Extracts by Inductively-Coupled Plasma with Mass Spectrometric Detection (ICP-MS)

- Instrument and analysis conditions should be optimized to achieve required sensitivity.
- Screen elements identified in ICH Q3D and USP <232>; where applicable, include silicon, tungsten and any additional elements known/suspected to be present in study material.
- The target level of Limit of Detection (LOD) is 20 ppb. The LOD may be lower or higher than 20 ppb depending on the element being detected, the sample matrix, and instrument parameters used. When the LOD is higher than 20 ppb, a justification should be provided.
- Report the LOD obtained for each element detected.
- Limit of Quantitation (LOQ) should be reported.
- Standard solutions containing detected elements should be used for recovery study; the recovery should be from 80 to 120%.
- Quantify the detected elements based on calibration curves.
- For the elements that have concentrations higher than DL, report the concentrations and µg/cm2.
- For the elements that are below DL, report the DL and indicate ND (not detected).
- Control sample injections should be run to subtract matrix associated elements from consideration.

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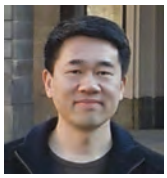

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ISPE Trains MHRA

by Christopher Potter and Bryan Wright

This article summarizes the agenda, targeted training requirements, and learning objectives from three ISPE training programs conducted at MHRA.

Background

ISPE approached the UK Medicines and Healthcare products Regulatory Agency (MHRA) to see if they were interested in an ISPE team of subject matter experts delivering a two day training program covering implementation of Quality by Design (QbD) as described in ICH guidelines Q8, Pharmaceutical Development[1] and Q11, Development and Manufacture of Drug Substances,[2] which also require application of Q9, Quality Risk Management[3] and Q10, Pharmaceutical Quality System.[4] It was proposed that this training program should be delivered to a mixed group of assessors and inspectors so that each group could understand better the issues faced by the other group. During discussions to arrange this QbD training, MHRA asked ISPE if it could deliver a one day training program on the recently-introduced EU guideline, Good Distribution Practice of Medicinal Products for Human Use[5] to Good Distribution Practice (GDP) inspectors, particularly training in application of quality risk management as discussed in section 1.5. Additionally, the MHRA also requested a one day training program for GMP inspectors on the application by industry, using case studies, of quality risk management as applied as part of GMP in manufacturing operations, for example, application of QRM during release by a qualified person. In both these latter cases, ISPE confirmed that teams of subject matter experts were available and enthusiastic to deliver the training. Dates were arranged in June 2013 for GDP training, October 2013 for GMP training, and February 2014 for QbD training.

Introduction

In the past year, ISPE has delivered the following three training programs to MHRA:

- Quality Risk Management to Good Distribution Practice (GDP) inspectors
- Quality Risk Management to Good Manufacturing Practice (GMP) inspectors
- Implementation of Quality by Design (QbD) to GMP inspectors and quality assessors

Each session was designed to be very interactive, allowing time for questions and discussion. Key training points were highlighted and exemplified during each program.

Existing ISPE material was used directly or after adaption to fit the program. For QbD training, significant material was taken from the following ISPE Guide Series: Product Quality Lifecycle Implementation (PQLI®) from Concept to Continual Improvement:

- Part 1 – Product Realization using Quality by Design (QbD): Concepts and Principles, including Overview, Criticality, Design Space, and Control Strategy[6]
- Part 2 – Product Realization using Quality by Design (QbD): Illustrative Example[7]
- Part 3 – Change Management System as a Key Element of a Pharmaceutical Quality System[8]
- Part 4 – Process Performance and Product Quality Monitoring System[9]

MHRA attendees were given access to these Guides.

Delivery and Learning Points

Training of GDP Inspectors

Thirteen inspectors were present – 11 from MHRA and two representing PIC/S; one from Finland and one from Eire.

MHRA feedback was that the session was very good and worthwhile and gave practical examples for use with objectives delivered. Reactions from participants included that the session provided:

GDP	GMP	QbD
Hanna Kviat Antonsen, NovoNordisk Mette Kræmmer Hansen, NovoNordisk Simon White, Pfizer Chris Potter, ISPE Advisor Bryan Wright, ISPE Advisor	Lynn Bryan, Consultant and ISPE UK Chair John Parker, AstraZeneca Rob Walker, Consultant Chris Potter, ISPE Advisor Bryan Wright, ISPE Advisor	Penny Butterell, Pfizer Graham Cook, Pfizer Bruce Davis, Consultant Line Lundsberg, NNE Pharmaplan Frank Montgomery, AstraZeneca Chris Potter, ISPE Advisor Bryan Wright, ISPE Advisor

Table A. ISPE Training Teams.

ISPE Trains MHRA

Continued.

- How QRM is incorporated into everyday GDP
- A basic knowledge of QRM and how to put it into practice
- Pragmatic use of QRM tools
- How to apply QRM to inspections of companies of all different sizes
- Lots of interaction
- Good engagement
- A dynamic group
- Both industry and regulators are learning
- As expected, there is different emphasis between industry and regulators in terms of what inspectors should do and what industry would like.
- Although the industry background presentation felt a bit remote to the presenter, it provided good background material, and if this course is to be delivered to other GDP inspectors, it should be retained.
- Consideration should be given to splitting the day in two half days to facilitate travel and help maintain energy levels

Course Objective		
Provide MHRA GDP Inspectors with: • A good understanding of ICH Q9, Quality Risk Management as it can be applied to GDP inspections • Practical exercises in applying QRM to GDP inspections • An understanding of some common pharmaceutical industry practices supporting distribution		
Session	**Agenda**	**Session Objective**
1.	Introductions	
2.	Objective of the Training	See above
3.	Individual Expectations	To capture expectations from the course from all attendees
4.	Presentation: Introduction to ICH Q9, Quality Risk Management – as applied to GDP	
	To give the inspectors an overall understanding of the purpose of QRM in general and in a GDP context as well as knowledge of the basic elements in QRM as outlined by the ICH Q9 Flowchart	
5.	Presentation: Overview of Typical Industry Practices	
	To describe packaging selection (stability, tamper-evidence, child proof), storage (Mean Kinetic Temperature principles, excursions, development studies), transport (simulations, development studies), selection of distribution companies, policies within company	
6.	Presentation: Seminar on QRM Tools	To give the inspectors an overview of tools and methods used with focus on the Fishbone diagram and FMEA/FMECA tools, as these are frequently used in larger companies
7.	Case Study	To familiarize the inspectors with the tools (Fishbone and FMEA) and deal with the typical challenges that arises when performing risk assessment as well as how outcome of a risk assessment (mitigation actions) can affect other parts of the Distributors Quality System
8.	Case Work	To prepare a risk assessment of part of a distribution chain – refer back to previous lecture where asked question – where does QRM apply?
7.	Discussion	Based on knowledge gained today, Inspectors to have time to start to write up and plan important areas of focus when reviewing a wholesalers approach to QRM
8.	Review of the day	Review against expectations

Table B. Agenda for training MHRA GDP inspectors in Quality Risk Management.

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ISPE Trains MHRA

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Training of GMP Inspectors

About 30 inspectors attended the training course. This training was constructed in a very short timeline and feedback was good with objectives of the training course achieved. Reactions from participants included that the session provided:

- Application of QRM in the real world
- A better understanding of the wider application of QRM in industry and established expectations for when inspecting
- A better understanding of how industry applies quality risk management
- Practicalities of QRM techniques
- Aspects of QRM to focus on during inspection
- Practical application of QRM principles – especially in smaller companies

Training of Assessors and Inspectors in QbD Implementation

A total of about 40 regulators were present consisting of about 15 inspectors and 25 assessors.

Feedback from this training course was excellent. A particular benefit was that the training course provided a good opportunity for assessors and inspectors to work together and interact, and both groups indicated that they particularly found this aspect to be of value.

The program did capture what regulators would like in a submission, which contains in part, science and risk-based elements (a QbD submission). A summary for the benefit of industry is:

Course Objective		
Provide MHRA GMP Inspectors with: • Practical applications of quality risk management, i.e., considerations and possible impact of QRM on quality management system, qualified person batch release, supply chain management, vendor assurance, validation (process, facilities, equipment) • QRM tools – the applications and limitations of QRM tools • Introduction to statistical tools used to monitor process performance		
Session	**Agenda**	**Session Objective**
1.	Introduction	
2.	Quiz on Terminology and Abbreviations	Interactive starter
3.	Presentation: ICH Q9, Q10 and QRM	Reintroduce principles of Q9 and touching on Q10, and Chapter 1 GMP Guide
4.	Presentation: Practical Application by Industry	To give the inspectors using real practical examples an overview of how industry is applying QRM tools in GMP systems and their limitations
5.	Presentation: Overview of Statistical Tools Used in QRM and their Practical Application by Industry	To give the inspectors an overview of how industry is deploying statistical methodology to enable a more objective assessment of data used in the identification and evaluation of risk including their limitations
6.	Presentation: Overview of the Methodologies used by Industry to Analyse and Evaluate Risk	To give the inspectors an understanding using real examples of the methodologies used by industry to quantify risk and to prioritize risk mitigation strategies highlighting how the inherent subjectivity associated with these methods can be minimized
7.	Exercise/Workshop: The Assessment Process and Practical Exercises for Case Study Discussion and Presentation	Case Studies: • Vendor Assurance • Cleaning Validation • QP Release Each group to present in terms of what the risk was/what they did/ what was the tool used, and why/what risk mitigation they did/what risk acceptance they took on board/ how they selected their team and how they wrote up and communicated the QRM process
8.	Discussion: Applications of QRM from ISPE Members	To discuss examples to provide greater understanding
9.	Quiz and Conclusion	

Table C. Agenda for Training MHRA GMP inspectors in Industrial Practice of Application of Quality Risk Management.

ISPE Trains MHRA

Continued.

- Companies should use ICH terminology. Use of "in house" terminology, even if explained, serves to make work more difficult for regulators.
- A submission should contain a compelling story with clear explanation of how risks are determined and reduced. For example, there should be explanation why "red" risk are changed to "green." The story should be succinct and not only include raw data.
- If companies train staff well in use of QRM terminology and regula-

Course Objective		
For MHRA Assessors and Inspectors: • To demonstrate the implementation and highlight the differences when companies use integrated science and risk-based approaches described in ICH Q8, Q9, Q10 and Q11 to: - Develop new products and processes - Implement continual improvements • To apply the principles in workshop exercises to: - Further develop understanding of the practical aspects of implementation - Reinforce the principles underlying different implementation practices		
Session	**Agenda**	**Session Objective**
1.	Introductions	
2.	Presentation: Refresher of principles of Q8, Q9, Q10 and Q11, including interaction and illustrated by practical examples of implementation and impact of product lifecycle	Brief refresher to ensure audience has consistent level of understanding
3.	Exercise/Workshop – QRM in Decision-Making/Calibration of Risk Usage Across Group.	To introduce different applications, different levels of risk "appetite" and how availability/consideration of data and appropriate application of Q9 can influence risk assessment outcome To determine how to use science and risk (e.g., inspection frequency, inspection preparation, dossier review)
4.	Presentation – Application of Q9 and Q10 in Lifecycle Management, Giving More Emphasis to Q9.	To provide examples of application and limitations of some QRM tools in a pharmaceutical quality management and how quality culture impacts both appropriate application and potential limitations
5.	Presentation – Product and Process Development – What is Different With Best Practice Implementation Examples	To enhance understanding of challenges and opportunities afforded by application of QbD principles (e.g., QRM) in development using industry examples and experience to date. Practical understanding how criticality is assigned (e.g., using QRM) and how this impacts product and process characterization studies
6.	Exercise/Workshop – Define Critical Quality Attributes (CQAs), Critical Process Parameters (CPPs) and a Control Strategy Based on Development Data for PaQLInol, an ISPE Fictitious Example	To provide practical knowledge of how a control strategy is developed and ranges defined and how it can be proposed and presented in a submission Understand what is new in a submission that may impact on inspection Understand the limitations of CTD format for QbD submissions
7.	Discussion Topic: What Differences do Inspectors and Assessors see When QbD/QRM are Implemented?	To develop further understanding
8.	Exercise/Workshop – QRM Implementation Throughout the Lifecycle	To enhance understanding of use of risk assessment tools and how appropriate choice of tool is key both to effective decision making and ensuring level of effort is commensurate with risk Gain understanding of QRM as it is applied in development and post-approval

Table D. Agenda for Training MHRA Assessors and Inspectors in Implementation of Quality by Design.

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tors recognize this competence, regulators have increased level of confidence in that company.
- Companies should demonstrate that they understand statistics and mathematical models included in submissions and explain the implications of their use and conclusions.
- Regulators are suspicious when there are very few or not any CQAs or CPPs.
- Regulators would like companies to use a peer review process for their submissions so that a person independent from the project team (an "expert") reads the dossier to ensure that a cohesive story is presented.

There are some issues that require industry and regulators to achieve a more common understanding. Perhaps the biggest issue is for industry and regulators to develop a more common understanding of risk. For example, regulators would like more consistent risk assessment exercises within and between companies, a task which companies indicate is extremely hard, if not impossible to achieve. The link between the output of risk assessment exercises and criticality assignment for CQAs and CPPs continues to be difficult, the continuum of risk being a concept that is hard to understand and put into practice.

Conclusion

ISPE has successfully delivered three different training programs and the material from these could be used for training other regulatory agencies.

Acknowledgements

ISPE would like to thank the subject matter experts listed in Table A and their companies for the enormous efforts, commitment of time and expertise to preparation and delivery of material. Additionally, ISPE would like to thank the following MHRA leadership for contributing to development of agenda, and making excellent arrangements for each of the training sessions:

- Saima Ahmad, Senior GMDP Inspector and Inspectorate Training Manager
- Malcolm Dash, Expert Pharmaceutical Assessor and Deputy Unit Manager, PLAT 4 and OTC
- Elena Razzano, Pharmaceutical Assessor

References

1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline,

Session	Agenda	Session Objective
9.	Presentation: Commercialization – Best Practice Implementation Examples	To demonstrate how a Q10 quality system is essential to effective transfer of knowledge from development to the commercial manufacturing environment, the inter-linkage of control strategy and design space and how QRM can be used to define the scope of equipment and process validation, based on current process understanding and the control strategy
10.	Exercise/Workshop – Develop a PV Strategy for PaQLInol Based on Development Data and Control Strategy	To learn how a validation study can be customized to focus appropriately on those aspects of a process where there is highest risk and reduce the level of effort required where there is lower risk
11.	Presentation: Commercial Manufacturing – Lifecycle Management	To demonstrate the lifecycle management of process knowledge during commercial manufacturing To identify differences from current approach To show how all parameters and attributes are managed at an appropriate level based on science and risk
12.	Exercise/Workshop: Establish a PPPQMS – Defining Scope, Reviewing Data, Updating Process Knowledge and Identifying CAPAs (e.g., Modifying Control Strategy). Evaluate A Change and Conduct a Deviation Investigation, Including CAPAs and how to Manage Knowledge Gained	To gain hands-on experience of what to expect in a process performance system, e.g., how current process understanding is used to make science- and risk-based decisions to support implementation of a change and to determine impact of a deviation
13.	Q&A	Opportunity to ask questions and have discussion
14.	Wrap-Up and Key Take-Away Messages	

Table D (continued). Agenda for Training MHRA Assessors and Inspectors in Implementation of Quality by Design.

ISPE Trains MHRA

Continued.

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8. *ISPE Guide Series: Product Quality Lifecycle Implementation (PQLI®) from Concept to Continual Improvement, Part 3 – Change Management System as a Key Element of a Pharmaceutical Quality System,* International Society for Pharmaceutical Engineering (ISPE), First Edition, June 2012, www.ispe.org.
9. *ISPE Guide Series: Product Quality Lifecycle Implementation (PQLI®) from Concept to Continual Improvement, Part 4 – Process Performance and Product Quality Monitoring System,* International Society for Pharmaceutical Engineering (ISPE), First Edition, June 2013, www.ispe.org.

For more information on the ISPE Guide Series: Product Quality Lifecycle Implementation (PQLI®) from Concept to Continual Improvement, please visit: www.ispe.org/pqli-guides.

Three Impressive Keynotes Address ISPE Annual Meeting Delegates

The Opening Session on Sunday, 12 October featured John Bournas, ISPE's President and CEO and Dinesh Thakur, Executive Chairman of Medassure Global Compliance Corporation.

ISPE's new President and CEO, John Bournas, told attendees that he was drawn to ISPE because of the organization's global efforts in preventing drug shortages.

"I look forward to listening to you, our key stakeholders, and establishing a close working relationship as we address our common challenges and opportunities," said Bournas.

Bournas referred to the impending release of the ISPE Drug Shortage Prevention Plan on Oct. 14 and commended the Plan Task Team and volunteers for their hard work on the Plan and added that continuing working to prevent drug shortages was high on his agenda.

"I decided to join your cause, which is also my cause, and is truly our cause," he said. "That cause is to offer patients a sense of security for a reliable and continuous supply of medications that are so significant to them and their families. I strongly encourage you to look at the valuable insights in this plan, which includes strengthening the integrity of the supply chain, and those sections that describe how to place a greater emphasis on quality that can make a real difference in the lives of patients."

Dinesh Thakur spoke on securing the supply chain and combating the significant and evolving risks in pharmaceutical sourcing and manufacturing. He pointed out that just over the last year and a half there have been large spikes in regulatory actions, particularly in batch failures, 483s, and problems with data integrity, all of which has increased supply chain risk. He cited both China and India as problem areas, but focused on India and asked if root causes could be understood and if what was going wrong could be fixed?

"Data integrity is a big concern," said Thakur, noting that the increase in regulatory actions in India has significantly spiked over the last three years.

In looking at the pharmaceutical industry in India he noticed trends in employee attrition in pharmaceutical companies in India and found a high annual attrition rate of 15 percent. He also investigated skill levels of both top management and lower levels; the lower level workers, he found, had little empowerment. Ultimately, he determined that "hierarchical attitudes in the pharmaceutical industry in India have played a significant role in creating quality problems."

He discovered that the significant quality problems have resulted from the culture in the industry in India and that Western concepts of quality based on openness are ineffective in a culture based on hierarchy.

"You can't take what works in a culture of transparency and get it to work in a culture that is opaque," said Thakur, noting that the quality problem did not exist to this degree three years ago. "The absence of a quality culture and the high cost of remediation have created the *perfect storm*."

Shail Thaker, Partner, McKinsey and Co., addressed delegates on Monday, 13 October by featuring "A Shot in the Arm: Coping with Change Fatigue in Pharma." "Change is proving hard for us as an industry," said Thaker, who noted that other industries, such as the communications, automotive, semi-conductor, and more recently the banking industry, have gone through profound yet successful fundamental transformations in recent decades. Those industries, he said, went through and achieved transformations, the hallmark of which has been "a structural shift."

So where does that put pharma? He cited two elements crucial to organizational change: "performance" and "health." Performance he suggested is what is "delivered," while the health of an industry involves alignment to execute and the ability to self-renew. "How has pharma been doing?" he asked while looking at 32 'activities' that would indicate organizational health. "It's not the picture of health." He reduced those 32 items to five important realities that did not reflect a picture of health for any industry and did not bode well for success, and then focused attention back on pharma.

First, a declining sense of direction is not good. Equally undesirable is, second, a radical shift in leadership styles with a decrease in "supportive" style, the opposite of "authoritarian" style. Third, a significantly increased 'inward focus' is not a good sign. It detracts from the customer focus.

"Taking a burdensome approach to managing key processes, such as compliance, is fourth," said Thaker. "Fifth among the signs of struggle is an underinvestment in managing change itself."

He said that in pharma there has been a consistent underestimation of what is required to make change happen. Although he claimed not to have a "silver bullet' to drive successful change, Thaker suggested sticking to your change 'story'; being disciplined for transformation; delivering meaningful simplifications; and 'hardwiring' a focus so that the focus is more than rhetoric.

"Health is not hard to measure," he concluded. "When you are dealing with change, do it with discipline and do it well."

2014 Award Winners Recognized at ISPE Annual Meeting

The 2014 International Honor Awards were announced during the ISPE Membership Luncheon on Tuesday, 14 October to ISPE groups and Members who have contributed remarkable service. The ISPE International Honor Awards Committee reviews nominations and administers the awards process. Thank you to Tim Howard and his Committee for doing a great job in identifying the honorees. Congratulations to the following:

Undergraduate Student Poster of the Year
Francesca Lynn
North Carolina State University
Carolina-South Atlantic Chapter

Graduate Student Poster of the Year
Jack Morel
University of California – Davis
San Francisco/Bay Area Chapter

Roger F. Sherwood Article of the Year
Chemical and Media-Free Pretreatment for Biopharma RO – Electrolysis for Scale Precipitation and UV Dechlorination
July/August 2014 Volume 34, Number 4
Nissan Cohen and Shlomo Sackstein

Affiliate and Chapter Excellence Award
ISPE Nordic Affiliate
ISPE Carolina-South Atlantic Chapter

Committee of the Year
Process Validation Statistics Conference Team

Chair	Joanne R. Barrick, RPh
Co-Chair	Jenn Walsh
Committee Member	James Bergum, PhD
Committee Member	Christopher C. Breen
Committee Member	Karthik B. Iyer
Committee Member	Mark D. Johnson
Committee Member	Markus Kiefer, PhD
Committee Member	Tara Scherder
Committee Member	Wendy Zwolenski-Lambert
Committee Member	Kimberly E. Vukovinsky

Company of the Year
Genentech (A Member of the Roche Group)

Max Seales Yonker Member of the Year Award
Michael L. Rutherford

Richard B. Purdy Distinguished Achievement
Arthur D. Perez, PhD

Joseph X. Phillips Professional Achievement Award
Nancy S. Berg

ISPE Plan to Prevent Drug Shortages

ISPE released its Drug Shortages Prevention Plan on 14 October at the 2014 Annual Meeting. The ISPE Drug Shortages Task Team developed the Plan in response to global regulatory interests in a collaborative action plan aimed at preventing drug shortages due to manufacturing and quality issues. The Plan lays out how industry can best prevent drug shortages from occurring by identifying the root causes of supply disruptions and creating a quality culture that will ensure a robust, resilient and reliable supply of medications – some life-saving – to patients worldwide.

"ISPE's Drug Shortages Prevention Plan is part of a significant and continuing effort since 2011 to ensure a safe, quality and reliable drug supply," said ISPE President and CEO John Bournas at the Plan's release in a special session. "We owe patients a sense of security by meeting their expectations for a reliable and continuous supply of the medications that are so important to them and their families. When members of the pharmaceutical industry discover and put to work the valuable insights included in the Plan, particularly those promising to strengthen the integrity of the supply chain and those describing how to place a greater emphasis on end-to-end quality, a real difference can be made in the lives of patients."

ISPE shares the sense of urgency expressed by regulators, pharmacy groups and patients and commits to publicizing and making this work widely available. The complete ISPE Drug Shortages Prevention Plan is available at www.ispe.org/DrugShortagesPreventionPlan.

The Plan builds on the results of ISPE's 2013 Drug Shortages Survey that cited manufacturing quality issues as a major cause of drug shortages. This Plan is global in nature and represents a continuum of work done to date supporting the US FDA's Strategic Plan for Preventing and Mitigating Drug Shortages and ongoing communications with other health authorities, such as Health Canada and Japan's Pharmaceuticals and Medical Devices Agency (PMDA).

"In 2012, a drug shortage crisis developed in many parts of the world, including the US," said Donna Gulbinski, Senior Vice President Global Quality and Environmental Health at Bristol-Meyers Sqibb and member of the ISPE Task Team. "We knew that quality manufacturing issues were a root cause, but drilling down farther we found other elements, such as equipment, raw materials and facility manufacturing problems. The Plan recommends that firms build a corporate goal around product quality and make building a Corporate Quality Culture the responsibility of everyone, from the CEO to the shop floor."

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ISPE Process Validation (PV) Team Provides Answers to Frequently Asked PV Lifecycle Approach Questions

The ISPE PV team consists of approximately 65 members from across industry manufacturing firms and other subject matter experts. It strives to assist industry with suggestions for and examples of practical implementation of the lifecycle approach to process validation. The team delivers conferences, discussion forums and discussion papers on various aspects of this topic. The issues to address have been prioritized and address what the team agrees are the most significant changes and challenges. It has become apparent through recent conferences that awareness of these discussion papers, which are available free of charge to members on the ISPE website, is not widely known. Many questions frequently asked at conferences, etc., are addressed in these documents and the list below identifies a few of the FAQs addressed by each paper. Please note that these are not consensus standards, but are intended to provide starting points for discussion and application at individual companies. Papers can be found by accessing the following link: http://www.ispe.org/publications/discussion-papers or by going to the ISPE website, accessing the "Knowledge and Learning" button at the top, clicking on "publications," and then clicking on "See All Discussion Papers."

Below, please find examples of questions and discussion papers which may help to provide answers:

1. **How many batches should be included in the process validation exercise? How can science and risk be utilized in determining the number of PV Batches?** – see discussion paper Topic 1 – Stage 2 Process Validation: Determining and Justifying the Number of Process Performance Qualification Batches.

Note: a second paper with additional approaches is under development.

2. **Is enhanced sampling and testing always needed as part of continued (ongoing) process verification subsequent to the validation exercise? How can a science and risk assessment be utilized to determine which Critical Quality Attributes, if any, should be tested at a heightened level?** Discussion paper Topic 2 – Stage 3 Process Validation: Applying Continued Process Verification Expectations to New and Existing Products.

3. **Does the lifecycle approach to PV apply to Biotech products?** Discussion Paper Topic 3 – Lifecycle Approach to Biotech Process Validation.

4. **What are some of the statistical tools that might be applied during the validation lifecycle? When is it appropriate to use each statistical tool?** Discussion Paper Topic 4 – Evaluation of Impact of Statistical Tools on Process Performance Qualification (PPQ) Outcomes.

5. **What actions will facilitate smooth implementation of the lifecycle approach to PV at contract manufacturers?** A discussion paper has been developed on this topic and is undergoing final editing before posting on the ISPE website.

In additional to the supplement to the number of initial PV batches paper, the team is also developing discussion papers on the following PV topics:

- Application of Lifecycle PV Approaches to Legacy/Existing Products.
- Selecting Process Design/Development Batches to be Analyzed along with the Initial Process Validation Data (planned for the near future).

The second annual Statistics in Support of the Lifecycle Approach to PV Forum will be held on 14-15 April 2015 in Silver Spring, MD. Later in the 2015 year, the third annual Lifecycle Approach to PV conference will be held 6-7 October, also in Silver Spring. Watch the ISPE website for more upcoming detail, agendas and registration information.

ISPE Plan to Prevent Drug Shortages

Continued from page 93.

In creating the Plan, the Task Team engaged with leadership from more than 30 major pharmaceutical companies and included input from experts from several pharmaceutical associations, including the Association of the European Self-Medication Industry (AESGP), the European Federation of Pharmaceutical Industries and Associations (EFPIA), the European Generic Medicines Association (EGA), the Parenteral Drug Association (PDA), and the Plasma Protein Therapeutics Association (PPTA).

"I want to extend congratulations to ISPE's Task Team," said Douglas Throckmorton, MD, Deputy Directory, Regulatory Programs, FDA/CDER. "We reviewed the plan and ISPE is playing a terrific role in identifying sources for drug shortages, but there remains a lot to know. Cooperation between industry and regulators is essential to preventing shortages before they occur, and the Plan highlights the value of cooperation for us to continue making progress in preventing drug shortages."

Brendon Cuddy, Scientific Administrator, European Medicines Agency, also reviewed the plan. "I want to thank the ISPE team for their hard work in response to a challenge EMA laid down last year," said Cuddy. "There are a plethora of reasons behind drug shortages. The supply chain is complex and we know that at every stage there is an opportunity for a problem to arise."

The Plan, said Cuddy, may make it possible to shift from being reactive to proactive and prevent drug shortages before they occur. "The Plan uses the word "resilience," and that is a good word to describe a key aspect of what we are trying to achieve," explained Cuddy. "It means being able to withstand the shock, but it also refers to the ability to bounce back."

ISPE organized the Plan around a "six dimension" framework comprised of: Corporate Quality Culture; Robust Quality System; Metrics; Business Continuity Planning; Communication with Authorities; and Building Capability. In each chapter, the Plan provides answers to questions posed within each of the six dimensions, and also offers "real world" case studies that illustrate successful strategies to avoid supply disruptions and shortages.

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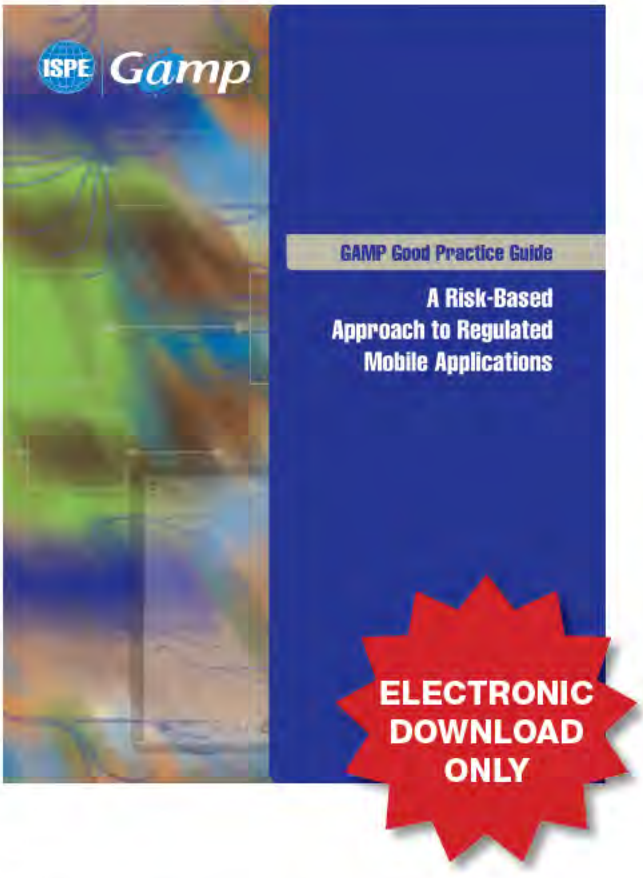

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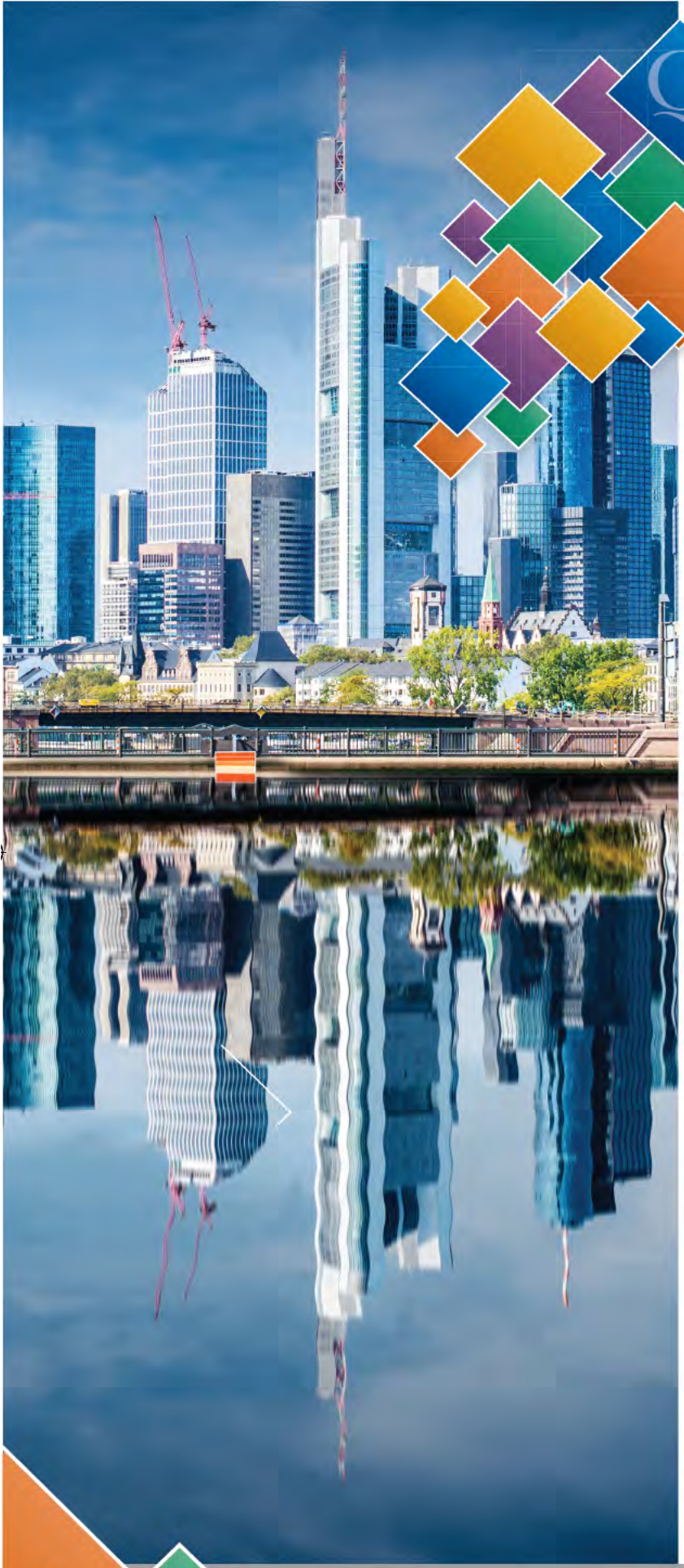

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